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1. Introduction

1.1 High mortality in dialysis patients
Dialysis patients have extraordinarily high mortality rates. Cardiac disease is the major cause of death accounting for 43% of all-cause mortality among patients receiving hemodialysis and peritoneal dialysis [Henry et al., 2002; US Renal Data System Annual Data Report Bethesda, 2005]. In previous report, patients with end-stage kidney disease (chronic kidney disease (CKD) stage 5) on dialysis, in comparison with the general population, also have a 3- to 30-fold increase in mortality, depending on the age group examined, and cardiovascular disease accounts for more than half of all deaths, with myocardial infarction, ischaemic cardiomyopathy, stroke and peripheral vascular disease making up the bulk of deaths (Foley et al., 1998). The marked excess in cardiovascular mortality in CKD, compared with the general population, is not explained by the presence of traditional Framingham risk factors, such as diabetes, smoking, hypertension and elevated cholesterol levels (Zoccali, 2000; Longenecker et al., 2002). With vascular calcification and arterial stiffness being observed in young and middle-aged dialysis patients without conventional cardiovascular risk factors (London et al., 2003), the search for non-traditional risk factors has led to increasing evidence of a multitude of factors that contribute to ectopic calcification in CKD.

1.2 High mortality rate and hyperphosphatemia
Inorganic phosphate (phosphate) retention, or hyperphosphatemia, has been identified as playing a major role in the progression of renal failure and in the generation of secondary hyperparathyroidism and uremic bone disease (Slatopolsky et al., 2002). Further observational data have also shown a significant association of hyperphosphatemia with increased mortality among patients who have end-stage kidney disease and are on hemodialysis (Block et al., 1998; Owen & Lowrie, 1998; Ganesh 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). Elevated phosphorus and Ca × P are also independent risk factors for all-cause and cardiovascular mortality in CKD stage 5, and increased levels of parathyroid hormone may be associated with both cardiovascular disease and increased
vascular calcification (Braun et al., 1996; Block et al., 1998; Ganesh et al., 2001; Wang et al., 2003; Young et al., 2005). Thus, phosphorus has the potential to induce vascular calcification and may be cardiotoxic (Achinger & Ayus, 2006). Hyperphosphatemia is sometimes regarded as a distinct syndrome (Hruska et al., 2008), and its treatment should be considered preferentially and even independently of other laboratory values (Fig. 1).

![Diagram of the relationship between hyperphosphatemia and cardiovascular disease](image-url)

**Fig. 1. Hyperphosphatemia in hemodialysis**

### 2. Phosphate metabolism in human

#### 2.1 Phosphate metabolism in normal physiology

Phosphorus is essential for multiple and diverse biological functions, including cellular signal transduction, mineral metabolism, and energy exchange. Although more than 80% of total body phosphorus is stored in bone and teeth, intracellular phosphorus exists in the form of organic compounds such as adenosine triphosphate and as free anions like \( \text{H}_2\text{PO}_4^- \), which are commonly referred to as phosphate. Serum phosphorus primarily occurs in the form of inorganic phosphate, which is maintained within the physiological range by regulation of dietary absorption, bone formation, and renal excretion, as well as equilibration with intracellular stores (Takeda et al., 2000; Brinthurst et al., 2004; Fukagawa et al., 2004; Blumsohn, 2004).

Phosphate absorption in the renal proximal tubule and the small intestine is important for phosphate homeostasis. This is a major regulator of phosphate homeostasis and has the phosphate reabsorptive capacity to accommodate physiologic phosphate requirement. Up to 70% of filtered phosphate is reabsorbed in the proximal tubule where sodium-dependent
phosphate transport systems in the brush-border membrane mediate the rate limiting step in the overall phosphate reabsorptive process (Murer et al, 2000; Takeda et al, 2000; Miyamoto et al, 2007; Tenenhouse, 2005; Biber et al, 2009). Three different types of sodium-dependent phosphate transporters have been identified till now, types I, II and III. The sodium-dependent phosphate transport system includes the type Ila and type IIC Na-dependent phosphate cotransporters, which are localized in the apical membrane of the renal proximal tubular cells, and the type IIb Na-dependent phosphate cotransporter, which is localized in the apical membrane of the intestinal epithelial cells. The type IIa Na-dependent phosphate transporter is the major determinant of plasma phosphate level and urinary phosphate excretion (Murer et al, 2000; Takeda et al, 2000; Miyamoto et al, 2007; Tenenhouse, 2005; Biber et al, 2009). This transporter is regulated by physiological stimuli, for example, type IIa transporter levels in the apical membrane are increased in response to dietary restriction of phosphate and 1,25-dihydroxy-vitamin D$_3$ [1,25(OH)$_2$D$_3$] and decreased in response to parathyroid hormone, or a high-phosphate diet. In addition, intestinal phosphate transport activity and type IIb Na-dependent phosphate transporter levels are upregulated by 1,25(OH)$_2$D$_3$ (Xu et al., 2002; Segawa et al., 2004).

In addition, fibroblast growth factor 23 (FGF23), a recently identified member of the FGF family, is involved in renal phosphate homeostasis (Yu X & White, 2005; Yu & White, 2005). FGF23 induces urinary phosphate excretion by suppressing the expression of type Ila and IIC Na-dependent phosphate cotransporters in the brush border of renal proximal tubules (Shimada et al., 2004; Shimada et al., 2005). It also suppresses 1,25(OH)$_2$D production by inhibiting 1a-hydroxylase (CYP27B1), which converts 25-hydroxyvitamin D [25(OH)D] to 1,25(OH)$_2$D, and by stimulating 24-hydroxylase (CYP24), which converts 1,25(OH)$_2$D to inactive metabolites in the proximal tubule of the kidney (Shimada et al., 2004; Shimada et al., 2005). Given the fact that FGF23 promotes renal phosphaturia, its secretion should be regulated by serum phosphate levels. Experimental and clinical studies showed that several days of dietary phosphate loading lead to an increase in serum FGF23 in humans (Ferrari et al, 2005; Perwad et al., 2005; Nishida et al., 2006).

2.2 Phosphate metabolism in hemodialysis patients

Several studies have measured circulating FGF23 levels in predialysis and dialysis patients and reported progressively elevated FGF23 levels as serum creatinine or phosphate levels increase (Larsson et al., 2003; Imanishi et al., 2004). Thus, it appears that in patients with CKD, FGF23 production increases to counteract chronic phosphate retention by promoting urinary phosphate excretion in the face of reduced nephron mass. Notably, in this setting, a previous study showed that FGF23 was a strong independent predictor of diminished 1,25(OH)$_2$D levels, even after adjustment for renal function, serum phosphorus levels and 25(OH)D levels (Gutierrez et al., 2005). This finding suggests that in patients with CKD, increases in FGF23 intended to maintain neutral phosphate balance result in suppression of renal 1,25(OH)$_2$D production, thereby triggering the early development of secondary hyperparathyroidism (Fig. 1).

3. Cardiovascular disease in hemodialysis

3.1 Hyperphosphatemia and cardiovascular disease
Cardiomyopathy and ischemic heart disease including acute myocardial infarctions, which are both common conditions in dialysis patients, likely play a role in the development of
3.2 Vascular calcification

Phosphate is probably the predominant inducer of vascular calcification, and elevated serum levels are strongly associated with increased vascular calcification and mortality (Goodman et al., 2000). Elevated phosphate triggers a concentration-dependent precipitation of calcium in vascular smooth muscle cells, and phosphate is also a potent stimulus for the differentiation of vascular smooth muscle cells. In vitro studies demonstrate that high phosphate levels in incubation media enhance calcification with associated extracellular matrix synthesis (Jono et al., 2000). Phosphate and sodium dependent phosphate transporter seem to play a very important role in vascular smooth muscle cells mineralization. Type III sodium-dependent phosphate transporter presents two discrete subtypes, Pit-1 and Pit-2. In human vascular smooth muscle cells, Pit-1 is mainly expressed (London et al., 2000). Apatite formation by smooth muscle cells, as a response to increased phosphate levels, is fully inhibited by phosphonoformic acid (PFA), a sodium dependent phosphate transporter inhibitor, a finding supporting the notion that vascular calcification is an active rather than passive cellular process (Giachelli et al., 2001; Ketteler et al., 2003).

Hyperphosphataemia induces osteocalcin and Cbfa-1 in vascular smooth muscle cells and promotes vascular calcification. Animals deficient in Cbfa-1 fail to mineralize bone (Komori et al., 1997), and there is also increased expression of Cbfa-1 when vascular smooth muscle cells are incubated in uremic serum compared with pooled human serum (Moe et al., 2003). There is now considerable evidence that hyperphosphataemia regulates several signalling pathways of cell functions. Of great interest is the recent identification of a novel phosphate-regulating gene, klotho (Kuro-o et al., 1997; Yoshida et al., 2002), which in mice is involved in the development of a syndrome resembling human ageing. The klotho mutant mice show abnormal calcium phosphate vitamin D metabolism and develop hyperphosphataemia and vascular calcification (Kuro-o et al., 1997; Yoshida et al., 2002). Hyperphosphataemia also down-regulates klotho gene expression (Fig. 1).

3.3 Endothelial dysfunction

Endothelial dysfunction is the principal cause of atherosclerosis resulting in cardio vascular disease (Ross, 1999). High phosphate loading on endothelial cells inhibited nitrogen oxide (NO) production through increased reactive oxygen species (ROS) production and endothelial NO synthase (eNOS) inactivation via conventional protein kinase C, resulting in impaired endothelium-dependent vasodilation (Shuto et al., 2009). Furthermore, dietary phosphate loading can deteriorate flow-mediated vasodilation in healthy men, suggesting...
that dietary phosphate loading or elevation of serum phosphorus level may be a risk factor for cardiovascular disease in healthy persons as well as CKD patients (Takeda et al., 2006; Shuto et al., 2009). Di Marco et al. also reported that high phosphate loading increased ROS production via phosphate influx and induced apoptosis in endothelial cells (Di Marco et al., 2008). Association of serum phosphorus level and vascular dysfunction has been well investigated, because fasting serum phosphorus level could not increase in healthy persons, even if dietary phosphate was overloaded. However, postprandial phosphorus elevation was associated with %FMD in young healthy men (Shuto et al., 2009). Thus, dietary phosphate loading can cause endothelial dysfunction within a short time. Oxidative stress and decreased NO production in endothelial cells are possible mechanisms for the impaired endothelial function mediated by phosphate loading (Fig. 2).

Fig. 2. Dual pathways for vascular dysfunction caused by hyperphosphatemia

3.4 Arterial stiffness
Arterial disease observed in end-stage kidney disease patients is characterized by extensive intimal as well as medial calcification. Histological changes in coronary arteries from dialysis patients, compared with age matched controls, reveal a similar magnitude of atherosclerotic plaque burden and intimal thickness but markedly increased medial calcification (arteriolosclerosis) (Schwarz et al., 2000). Medial calcification has been shown to affect vascular elasticity and leads to increased arterial wall stiffness of large capacity, elastic-type arteries like the aorta and the common carotid artery, increased pulse pressure
and decreased perfusion of coronary arteries during diastole (Blacher et al., 1998; London, 2003; Speer & Giachelli, 2004). Recent studies also demonstrated that elevated FGF23 levels were associated with arterial stiffness, increased left ventricular mass index and increased prevalence of left ventricular hypertrophy in patients with CKD (Hsu & Wu, 2009; Mirza et al., 2009; Gutierrez et al., 2009).

4. Management of hyperphosphatemia in hemodialysis patients

4.1 Target of management

As elevated serum phosphorus and calcium levels are associated with vascular calcification and cardiovascular mortality in CKD, priority should be given to normalization of these parameters. It is generally accepted that adequate control of serum phosphorus remains a cornerstone in the clinical management of patients with CKD not only to attenuate the progression of secondary hyperparathyroidism but also possibly to reduce the risk for vascular calcification and cardiovascular mortality. A Ca $\times$ P more than 72 mg$^2$/dl$^2$ is associated with a significant increase in the relative risk (RR) of mortality (RR = 1.34) compared with Ca $\times$ P less than 50 mg$^2$/dl$^2$ (Cozzolino et al., 2001). In a study in patients on hemodialysis, those who did not experience valvular calcification had maintained Ca $\times$ P at an average of 51 mg$^2$/dl$^2$ in the 6 months prior to the study, while those who did experience valvular calcification had an average Ca $\times$ P of 60 mg$^2$/dl$^2$ (Ribeiro et al., 1998). The target of treatment should be to maintain serum phosphorus level less than 5 mg/dl with serum calcium level less than 10 mg/dl to prevent cardiovascular consequences. This will allow the maintenance of Ca $\times$ P less than 50 mg$^2$/dl$^2$, a level which available evidence has so far shown not to promote calcification or increase mortality (Ribeiro et al., 1998). High FGF23 levels are more strongly associated with kidney disease progression, left ventricular hypertrophy, vascular disease, and mortality than serum phosphorus levels, and were most predictive of adverse events in patients with normal serum phosphorus (Thadhani et al., 2008; Oliveira et al., 2010). Dietary phosphate binders can lower FGF23 in CKD (Oliveira et al., 2010). Management of hyperphosphatemia relies on dietary restriction, the use of phosphate binders and dialysis.

4.2 Dietary restriction of phosphate intake

The average diet in North America and Europe contains approximately 1,000 to 1,500 mg of phosphorus per day (Willett & Buzzard, 1998). Dietary approach to phosphate retention in advanced renal failure patients, dietary approach to phosphate reduction is an important step in the treatment of hyperphosphatemia. The level of expression of klotho mRNA was greatly reduced in the kidneys of all chronic renal failure patients. Dietary phosphate restriction induced klotho expression, which enhances the beneficial effect of phosphate restriction in patients with chronic renal failure and or on hemodialysis. However, dietary restriction cannot considerably reduce the level of phosphate retention. As dialysis patients tend to need higher levels of protein due to the losses via dialysis, tight restriction on phosphate is difficult without compromising a patient’s nutritional status. Because most dietary phosphate is contained in protein-rich foods, there is some concern about excessive protein restriction. In fact, the minimum amount of protein of 1.2 g/kg body weight/day, recommended to prevent malnutrition makes planning a diet with less than 1 g of phosphorus impossible (Kopple, 2001; Eknoyan et al., 2003). Recommendations that call for 1.0 to 1.2 g/kg/day protein will usually obligate a phosphorus intake of 800 to 1,400

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mg/day. Net phosphorus absorption averages 60% to 70% of intake (Delmez & Slatopolsky, 1992; Sheikh et al., 1989), however, this percentage can rise as high as 86% of ingested phosphate with calcitriol use and decrease to 30% to 40% of ingested phosphate with optimal binder usage (Sheikh et al., 1989; Delmez & Slatopolsky, 1992).

Other foods that are high in phosphate are processed foods such as processed meats which have phosphate based additives to improve the consistency and appearance of the food. Since 1990, intake of phosphate from additives has doubled and has been 1,000 mg in USA (Calvo & Park, 1996). This is the amount that some renal patients are advised for the whole day from all food groups (James & Jackson, 2002). As people are becoming more reliant on processed and packaged meals due to convenience, phosphate from these sources needs to be considered when advising on diet. Fresh meat is considered suitable for someone following a phosphate restriction, however processed foods may in fact be providing much more phosphate than realised (Sullivan et al., 2007). Beverages such as sodas, juices and sport drinks also contain phosphate additives (Murphy-Gutekunst, 2007). It has been estimated that for a person on hemodialysis the average phosphate removal per day is 300 mg (Vaithilingham et al., 2004). This leaves the patient with a positive balance for phosphate.

4.3 Hemodialysis
The clearance of phosphate varies among the different modalities of dialysis. Ideally, adequate dialysis in any form would remove adequate amounts of all uremic toxins, including phosphate. Unfortunately, conventional thrice-weekly hemodialysis (4 h duration) removes approximately 900 mg of phosphorus each treatment (an average of only 300 mg/day) (Gotch et al., 2003). Increasing the dosage of dialysis, preferably to lengthy three times per week dialysis, hemodiafiltration, or, even better, daily/nightly dialysis may prevent phosphorus retention and even require no dietary phosphate restriction or the withdrawal of phosphate binders (Maduell et al., 2003; Benaroia et al., 2008). However, regular dialysis treatment is not able to remove all the phosphorus ingested with a diet containing protein of 1.0 - 1.2 g/kg/day (Mallick & Gokal, 1999).

4.4 Phosphate binders
Isakova et al analyzed a prospective cohort study of 10,044 incident hemodialysis patients at Fresenius Medical Care facilities in 2004 and 2005 comparing 1-year all-cause mortality among patients who were treated with phosphate binders (Isakova et al., 2009). In an intention-to-treat analysis, they compared patients who began treatment with any phosphate binder during the first 90 days after initiating hemodialysis, with those who remained untreated during that period. Treatment with phosphate binders was independently associated with decreased mortality compared with no treatment. In the unmatched cohort, the phosphate binder-treated group had a relative risk reduction of 42%, while in the intention-to-treat and as-treated analyses, the magnitude of the survival benefit ranged between 18% and 30% in multivariate models. The association between use of phosphorus binders and survival was observed within each quartile of baseline serum phosphorus except the lowest. Results from human data suggest that lowering of phosphorus levels by intake of phosphate binders will substantially reduce serum FGF-23 levels (Koiwa et al., 2005; Pande et al., 2006). In this prospective observational study, treatment with phosphate binders was associated with a reduced 1-year mortality among incident hemodialysis patients (Isakova et al., 2009).
Sevelamer hydrochloride and lanthanum carbonate are phosphate binders containing neither calcium nor aluminium, and are useful in those being administered concurrent vitamin D to reduce the potential for hypercalcemia. Attenuation in the progression of coronary artery calcification, after 6 and 12 months, was shown in hemodialysis patients treated with sevelamer, with reduced serum calcium, compared with patients on calcium carbonate (Chertow et al., 2002). A more recent randomized study of 114 incident hemodialysis patients demonstrated a survival advantage for patients on sevelamer compared with calcium carbonate after 18-month follow up (Block et al., 2007). A further beneficial effect of sevelamer has been proved on markers of coronary artery and aortic calcification compared with calcium based phosphate binders (Chertow et al., 2002). The attenuation of vascular and, in particular, coronary calcifications compared with calcium-based phosphate binders in end-stage kidney disease patients under dialysis has been studied by electron beam computed tomography (Raggi, 2002; Raggi, 2004). High doses of sevelamer (3.2–8 g/day) are necessary to bring hyperphosphatemia back to target level, and the number of pills per day (about 8 x 800 mg tablets) may certainly be a conditioning factor for the patient’s compliance (Chertow et al., 2002).

Patients with end-stage kidney disease treated with lanthanum carbonate up to 2.5–3.8 g/day for up to 2 years have been reported to obtain effective reduction of serum phosphorus level (Finn, 2006). Lanthanum-carbonate-treated patients have, also been shown to reach a significantly reduced calcium/phosphate product and parathyroid hormone level compared with the placebo (Joy & Finn, 2009). Lanthanum carbonate, therefore, is an effective, at least as effective as calcium carbonate, well-tolerated phosphate binder (Hutchison, 2004; Hutchison et al., 2006). However, despite the very encouraging results, further studies involving larger numbers of patients are needed to definitively establish the long-term safety of lanthanum regarding tissue deposition, as well as its efficacy on vascular calcifications or outcomes in treated patients, which also need to be confirmed in the long term.

4.5 Combination in treatment

A multiple-factor approach can be used to reduce serum phosphate including reduced phosphorus intake in the diet, using phosphate binders efficiently and avoidance of under-dialysis. The patient's diet should be high in nutrition but with the lowest possible phosphorus content. Since dietary control of phosphorus intake and dialysis removal are usually not sufficient, phosphate binders are usually needed as adjuvants to increase fecal excretion (Bover et al; 2005). For an optimal protein diet of 1-1.2 g/kg/day, the phosphorus intake was 778-1,444 mg/day and 5,500-10,000 mg/week. Dialysis has limited ability for phosphate control, although phosphate removal by hemodialysis is very much a time-dependent process. The amount of phosphorus removed by hemodialysis, extrapolated to an average week, is 250-300 mg/day. The introduction of non-calcium-based phosphate binders has enabled a reduction in the total phosphate load and provides a useful tool in the prevention of vascular calcification in CKD. The use of phosphate binders may decrease the phosphorus absorbed from the diet to 40% (Llach & Bover, 2000). In these circumstances, 320 mg of phosphorus and 21g of protein (0.3-0.35g of protein/kg/day) intake should be the critical value above which a positive balance of phosphate may occur (Fig. 3).
Successful control of phosphate is one of the key aspects in the management of dialysis patients (Rodriguez-Benot et al., 2005; Young et al., 2004, Young et al., 2005). However, numerous studies have revealed the difficulty in achieving phosphorus targets less than 5.5 mg/dl (Arenas et al., 2006; Lorenzo et al., 2006; Wei et al., 2006), despite the wide variety of drugs available for its treatment (Joy & Finn, 2003; Sprague, 2007; Arenas et al., 2008). Both endothelial dysfunction and medial calcification are closely associated with development of cardiovascular disease. It is well known that long-term exposure to phosphate, generally observed in end-stage renal failure patients, can mediate vascular calcification (Jono et al., 2000; Giachelli, 2003). Dietary high phosphate loading can be involved in the postprandial elevation of serum phosphorus level, and this short-term exposure to phosphate was enough to decrease endothelium-dependent vasodilation.

5. Conclusion

The goals of therapy have been to reduce phosphorus intake with low protein diet and phosphate binders. Since low protein diet is thought to be induce malnutrition, it is thought that strict adherence to a low protein diet is not practical. A diet rich in proteins is usually also rich in phosphorus. However, proteins with very different phosphorus contents can provide equivalent nutritional value, as can be seen from the difference in phosphorus content between meat, cheese, and eggs. Egg white is an excellent example of food with a high level of protein but low phosphorus content. Moe et al. demonstrates the importance of
the protein source of phosphate in overall mineral metabolism after only 7 days of controlled diets. Despite equivalent protein and phosphorus concentrations in the diets, subjects had lower serum phosphorus levels, a trend toward decreased urine 24-hour phosphorus excretion, and significantly decreased FGF23 levels in the vegetarian diet compared with the meat-based diet (Moe et al., 2011).

Lafage et al. (Lafage et al., 1992) used a very low protein diet (0.3 g/kg/d) supplemented with amino acids and ketoanalogues and with only 1 g of calcium carbonate and 1,000 IU of vitamin D3 in 17 patients with advanced renal failure. They have shown not only a beneficial effect related to the control of hyperphosphatemia on the biologic and histologic parameters of hyperparathyroidism but also a correction of acidosis, which resulted in the disappearance of the osteomalacic component. Thus, dietary control often considered to be of minor importance, is actually one of the major keys to success in the management of hyperphosphataemia.

6. Acknowledgements

The work described in this publication was supported by Grants-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology in Japan (to ET, HY, and YT).

7. References


Hemodialysis (HD) represents the first successful long-term substitutive therapy with an artificial organ for severe failure of a vital organ. Because HD was started many decades ago, a book on HD may not appear to be up-to-date. Indeed, HD covers many basic and clinical aspects and this book reflects the rapid expansion of new and controversial aspects either in the biotechnological or in the clinical field. This book revises new technologies and therapeutic options to improve dialysis treatment of uremic patients. This book consists of three parts: modeling, methods and technique, prognosis and complications.

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