EVALUATION ON SELF-ADJUSTED PHOSPHATE BINDER ADMINISTRATION TO DIETARY PHOSPHATE CONTENTS IN MANAGEMENT OF HYPERPHOSPHATEMIA AMONG HEMODIALYSIS PATIENTS IN PENANG, MALAYSIA

KHOR SU MEE

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by

KHOR SU MEE

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LIST OF ABBREVIATIONS

BMI	Body Mass Index
Ca	Calcium
Ca x P	Calcium x Phosphate
CHD	Conventional Hemodialysis
CKD	Chronic Kidney Disease
CRC	Clinical Research Center
DOPPS	Dialysis Outcomes and Practice Pattern Study
eGFR	estimated Glomerular Filtration Rate
ECC	European Economic Community
ESKD	End State Kidney Disease
FGF 23	Fibroblast Growth Factor 23
GFR	Glomerular Filtration Rate
HBM	Hospital Bukit Mertajam
HBP	Hospital Balik Pulau and
HPP	Hospital Pulau Pinang
HSB	Hospital Sungai Bakap
HSJ	Hospital Seberang Jaya
HD	Hemodialysis
IDWG	Intradialytic Weight Gain
IQR	Interquartile range
KDIGO	Kidney Disease: Improving Global Outcomes
Kt/ V	Dialyzer clearance of urea x dialysis time / volume of distribution of urea
LOC	Locus of Control
M	Mean
MBD	Mineral Bone Disease
MDRD	Modification of Diet in Renal Disease
MEMS	Medication Event Monitoring System
MMAS-8	Morisky 8-item Medication Adherence Scale
MREC	Medical Research Ethic Committee
NGO	Non-Governmental Organizations
NHD	Nocturnal Hemodialysis
Npt	Sodium phosphate co-transporter
NS	Not Significant
P	Phosphate
PB	Phosphate Binder
Pc	Piece
PD	Peritoneal Dialysis
PEP	Phosphate Education Program
Pi	Inorganic Phosphate
P : P	Phosphate : Protein
PTH	Parathyroid Hormone
PU	Phosphate Unit
Qb	Blood flow
Q-Q plot	Quantile-Quantile plot
RCT	Randomized Control Trial
RM ANOVA	Repeated Measure Analysis of variance

SD	Standard Deviation
SDHD	Short Daily Hemodialysis
SHPT	Secondary Hyperparathyroidism
SPB	Self-adjusted Phosphate Binder
SPL	Serum Phosphate Level
Tbsp	Tablespoon
Tsp	Teasppon
USD	United State Dollar
USRDS	U.S. Renal Data System

PENILAIAN PENGUBAHSUAIAN SENDIRI DALAM PENGAMBILAN UBAT PENGIKAT FOSFAT MENGIKUTI KANDUNGAN FOSFAT DALAM MAKANAN UNTUK PENGURUSAN HIPERFOSFATEMIA DALAM KALANGAN PESAKIT HEMODIALISIS DI PULAU PINANG, MALAYSIA

ABSTRAK

Hiperfosfatemia ialah satu masalah serius yang menyebabkan kadar kematian yang tinggi dalam kalangan pesakit dialisis. Banyak kajian telah menunjukkan bahawa dialisis dan kawalan makanan sahaja tidak dapat menguruskan masalah hiperfosfatemia. Justerus itu, ubat pengikat fosfat biasanya diperlukan oleh pesakit dialisis. Kaunseling makanan yang sediada untuk mengamalkan diet rendah fosfat didapati tidak memberi kesan yang nyata untuk mengawal paras fosfat pesakit. Oleh itu, kajian ini dilakukan untuk menilai keberkesanan buku kecil intervensi baru yang melibatkan 80 makanan yang biasa dimakan oleh pesakit hemodialsis di Pulau Pinang untuk pengubahsuaian sendiri bagi ubat pengikat fosfat mengikuti kandungan fosfat dalam makanan. Terdapat 117 orang pesakit hemodialisis dari 8 unit dialisis di Pulau Pinang telah dipilih untuk menyertai kajian ini. Mereka dibahagikan secara rawak kepada kumpulan intervensi dan kumpulan standard. Pesakit-pesakit daripada kedua-dua kumpulan telah menerima kaunseling makanan yang sama tentang diet rendah fosfat secara individu, sedangkan kumpulan intervensi diberi satu kaunseling tambahan tentang pengubahsuaian sendiri untuk ubat pengikat fosfat. Paras fosfat telah diukur pada permulaan kajian, bulan ke-3, bulan ke-6 and bulan ke-9 bagi kedua-dua kumpulan. Keberkesanan cara pengubahsuaian sendiri ubat pengikat fosfat terhadap jumlah pengambilan kalori, protein dan fosfat; kepuasan terhadap makanan; dan pematuhan terhadap pengambilan ubat pengikat fosfat juga diukur

pada permulaan dan pada akhir kajian ini. Analisis statistik telah dijalankan dengan mengunakan SPSS melalui cara "repeated measured ANOVA", "independent t-test" and "pair t-test" bagi data yang bertaburan normal. Di samping itu, Wilcoxon dan Mann Whitney digunakan untuk data yang tidak bertaburan normal. Analisis menunjukkkan penurunan yang ketara untuk purata paras fosfat bagi kedua-dua kumpulan selepas kajian. Walau bagaimanapun, kumpulan intervensi menunjukkan penurunan paras fosfat yang lebih nyata (2.15±0.22 mmol/L ke 1.68±0.43 mmol/L) dalam tempoh yang lebih singkat (3 bulan) berbanding dengan kumpulan standard. Di samping itu, ia menunjukkan penambahan skor untuk kepuasan terhadap makanan and pematuhan terhadap pengambilan ubat pengikat fosfat untuk kumpulan intervensi jika dibandingkan dengan kumpulan standard ($p<0.05$). Walau bagaimanapun, ia tidak terdapat perbezaan yang nyata untuk jumlah pengambilan kalori, protein and fosfat untuk kedua-dua kumpulan sebelum dan selepas kajian. Kesimpulannya, konsep pengubahsuaian sendiri bagi ubat pengikat fosfat mengikuti kandungan fosfat dalam makanan memberi kesan yang positif dalam penurunan paras fosfat, kepuasan terhadap makanan dan pematuhan terhadap pengambilan ubat fosfat dalam kalangan pesakit hemodialisis.

EVALUATION ON SELF-ADJUSTED PHOSPHATE BINDER ADMINISTRATION TO DIETARY PHOSPHATE CONTENTS IN MANAGEMENT OF HYPERPHOSPHATEMIA AMONG HEMODIALYSIS PATIENTS IN PENANG, MALAYSIA

ABSTRACT

Hyperphosphatemia is a serious problem that is associated with high mortality rate among the dialysis patient. Many studies have revealed that the dialysis and dietary restriction are insufficient for managing hyperphosphatemia. Thus, phosphate binder is usually required for the dialysis patients. Current diet counseling on low phosphate diet did not effectively lower the phosphate level. Therefore, this study was designed to evaluate the effectiveness of a newly intervention booklet that contains 80 common eaten foods that allowed the Penang hemodialysis patients to self-adjusted phosphate binder administration to their dietary phosphate content. A total of 117 of hemodialysis patients from 8 dialysis centers in Penang state were recruited for the study. They were randomly divided into intervention and standard groups. All the participants from both groups went through the same diet counseling on low phosphate diet individually but the intervention group was given an extra counseling on the self-adjusted phosphate binder. The phosphate level was measured at the baseline, month 3, month 6 and month 9 for both of the groups. The effect of the self-adjusted phosphate binder to the total calories, protein, phosphate intake; food satisfaction; and phosphate binder adherence were measured at the baseline and at the end of the study. Statistical analysis was carried out by using SPSS with the method of repeated measured ANOVA, independent t-test and paired t test for data that normally distributed while the Wilcoxon and Mann Whitney for data that was

not normally distributed. The analysis showed significant reduction of mean phosphate level for both groups. However, the intervention group showed significant reduction (2.15±0.22 to 1.68±0.43 mmol/L) with shorter time period (3 month) compare to the standard group. Furthermore, there were significant higher increment of the score for food satisfaction and phosphate binder adherence in the intervention group as compare to the standard group ($p<0.05$). However, there were no significant change in total calories, protein and phosphate intake for both groups before and after the study. In conclusion, the self-adjusted phosphate binder to dietary phosphate intake concept gave a positive impact on lowering the serum phosphate level, food satisfaction and phosphate binder adherence in hemodialysis patients.

CHAPTER 1

INTRODUCTION

1.1 Hyperphosphatemia in Chronic Kidney Disease (CKD)

Hyperphosphatemia is a serious and pervasive problem which will lead to secondary hyperparathyroidism, renal osteodystrophy and vascular calcification among CKD patients (Block et al., 2004; Cannata-Andia & Rodriguez-Garcia, 2002; Coladonato, 2005). Numerous studies have demonstrated increased risk of morbidity and mortality due to the consequences of hyperphosphatemia (Block et al., 2004; Kuhlmann, 2006). Therefore, prevention and correction of hyperphosphatemia has become a major goal of treatment for the kidney failure patients. The recommended control target for the phosphate level at 0.8 – 1.45 mmol/L should be achieved to reduce the mortality rate among these patients (Kok, Ghazalli, Ching, Fan, & Liew, 2013).

Phosphate control in CKD patients can be achieved by 3 methods: i) phosphate removal by dialysis, ii) restriction of dietary phosphorus intake and iii) inhibition of gastrointestinal phosphorus absorption by using phosphate binder (PB) (Kuhlmann, 2006). Despite follow the dialysis schedule and adjust the dialysis parameters to improve the phosphorus removal, majority of the CKD patients still need to follow the diet restriction on phosphate intake and required PB to achieve the target phosphate level (Cannata-Andia & Rodriguez-Garcia, 2002).

High phosphate level commonly happens in dialysis patients especially when they are well nourished (Chiu et al., 2009). This is because the high protein food has high content of dietary phosphorus (Uribarri, 2009). If patients follow the Chronic Kidney Disease Guideline's recommendation of 1.0g – 1.2g protein/ kg body weight, the total phosphorus intake would be exceed the recommendation of less than 1000mg phosphate per day. Generally, this total phosphate intake is hardly to be remove by the 3 time per week; 4 hours dialysis schedule alone (Uribarri & Calvo, 2003). Therefore, the use of PB and restriction of total dietary intake of phosphate others than from high protein food like phosphate additive were crucial in achieving the target phosphate level among the dialysis patient (Cannata-Andia & Rodriguez-Garcia, 2002).

However, poor adherence to PB prescription is commonly happening due to pill burden (Chiu et al., 2009; Kuhlmann, 2006). Generally, the dialysis patients use many pharmacological agents to treat, correct or prevent concomitant disease (cardiac disease, high cholesterol, bone disease, endocrine disorders) or symptoms (sleeping disorder, restless legs, gastrointestinal discomfort). Studies revealed that 49% of the total oral medications (with an average range of 10-14 drugs daily) that used by the dialysis patients was PB (Chiu et al., 2009; Kuhlmann, 2006). According to the authors, this large amount of medications intake causes the patients skipped the PB intake (Chiu et al., 2009). Hence, prescribing a larger number of PB might not be an appropriate solution to hyperphosphatemia. It was more important to avoid PB dosing error than prescribe more PB to the patients. The PB dose should be taken respectively to the total amount of phosphate intake in each meals and snack (Chiu et al., 2009).

Besides the PB non adherence, the hidden phosphate additive in the processed food is another challenge for dialysis patient to achieve the target phosphate level. Phosphorus is the main component of many preservatives and additives salts in processed foods (Uribarri & Calvo, 2003). The processed meat and poultry products are shown to have almost 2-3 fold increase in phosphorus content as reported in food composition (Uribarri & Calvo, 2003). Normally, the dialysis patients have reached the upper limit of total daily phosphate intake due to the high protein food intake. Thus, the extra phosphate load from food additive will easily lead to the failure in phosphate control (Uribarri, 2009). Therefore, the dialysis patients need to avoid processed food to have better control of phosphate level.

Unfortunately, the dialysis patient's daily life is struggled with dietary restriction as well as poor appetite and sometime lack of energy to cook. They will chose to consume the processed foods which are very accessible, tasty, and cheaper than fresh and unprocessed healthy food (Noori, Kamyar Kalantar-Zadeh, et al., 2010). Generally, these processed foods require very little or no preparation and relatively with cheaper price at most of the places. All these processed foods together with high protein diet have further caused the difficulty for dialysis patients in achieving the recommendation of taking less than 1000 mg daily phosphate intake. Thus, this excessive phosphate intake causes the prescribed PB dose become inadequate to inhibit the phosphate absorption (Blaine, Chonchol, & Levi, 2014).

Indeed, more than 90%- 100% of the phosphorus additive is believed to be absorbed in the intestinal tract, as opposed to only 40-60% of intestinal phosphorus absorption from animal protein and 10- 30% from vegetarian protein (Kalantar-

Zadeh et al., 2010; N. Noori et al., 2010). This high bioavailability of phosphate additive has further increase the risk of phosphate burden among dialysis patients. Besides, there is lack of information on the type and the amount of phosphate additive that is added to the processed food. The manufacturers do not require reporting the phosphate additives in the food label (Kalantar-Zadeh et al., 2010). Consequently, patients have no way to know the type and the amount of phosphate additives that are added to the processed food.

1.2 Problem Statement

According to the 21th Report of the Malaysian Dialysis & Transplant Registry in 2013, only 27% of peritoneal dialysis (PD) patients and 15% of hemodialysis (HD) patients achieved the target phosphate level (0.8 -1.45 mmol/L). A total of 45% HD patients and 30% PD patients had phosphate level of more than 1.8 mmol/L (Kok et al., 2013). Most of these patients were prescribed with PB and calcium carbonate remains as the main PB for both HD (92%) and PD patients (85%) (Kok et al., 2013).

The routine management of hyperphosphatemia in most of the dialysis center in Malaysia is dietary and phosphate binder's intake education by the dialysis center's staff nurse. There is usually no dietitian or pharmacist in the dialysis center. Thus, dietary and PB intake education by dietitian or pharmacist are limited. Generally, patients will be given a list of high phosphate content foods and also a list of substitution food items with low phosphate content. They are informed to avoid

the high phosphate food by compliance with the low phosphate foods intake. Meanwhile, there is very limited education on the correct timing and texture to consume the PB. The patients will only have chance to get a proper counseling when they are admitted to the hospital where the dietitian and pharmacist are available.

In Germany, there was a recent developed innovative Phosphate Education Program (PEP) concept that was based on eye-estimation of the meal phosphorus content by a newly defined phosphate unit (PU) where 1 PU is equivalence to 100 mg phosphorus. Sixteen pediatrics with CKD were recruited in the study and they were educated for self- adjust PB dose based on their own meal's phosphorus content with individually prescribed PB/PU ratio (PB pills per PU) (Ahlenstiel, Pape, Ehrich, & Kuhlmann, 2010). The study revealed that the PEP concept helped the dialysis patients to control their phosphate level more effectively where it reduced mismatch of the PB dose to the dietary phosphate content.

However, the investigators in the above mentioned study did not consider the intestinal phosphate absorption and also the phosphate additive content in the food. They only considered the food from the same food group which had similar phosphate content (for instance, a 150 g serving size of any meat sort = 3 PU) (Ahlenstiel et al., 2010). Furthermore, to the best of our knowledge, currently no study had been conducted in adult dialysis patients on the use of self- adjust PB dosage to dietary phosphorus intake by individually prescribed PB/PU ratio. Therefore, there is a need to create a friendly self-adjust PB booklet (SPB) for better controlling of the phosphate level among the dialysis patients. The Phosphate Unit (PU) to meal phosphorus content that consider the intestinal phosphorus absorption

of inorganic phosphate additive and the organic phosphorus in natural food should be developed from the common eaten foods by the dialysis patients in the local setting. The tool will allow greater dietary flexibility, increase food satisfaction & reduce pill burden of PB for the dialysis patients.

A SPB was developed in the present study by using the idea of PEP concept. The SPB had more detail with the inclusion of the commonly eaten Malaysian's food (including processed/convenient food) with descriptive & common food measures. The food list was fitted to the number of PB tablets to be taken which was based on 1 PB = 100 mg intestinal absorption of phosphate. The phosphate content was adjusted for the phosphate additive and also the percentage of intestinal phosphorus absorption. All the phosphate food contents were referred to the 4th edition of Nutrient Composition of Malaysian Food (Tee E Siong, 1997) and Food Composition Guide Singapore (*Food Composition Guide Singapore*, 2003).

1.3 Objectives

1.3.1 General Objective

The primary objective of the study was to determine the effectiveness of the SPB in reducing the phosphate level between the intervention group and the standard group of hemodialysis patients.

1.3.2 Specific Objectives

a) To determine the effectiveness of SPB in managing the corrected calcium, calcium phosphate product (Ca x P product), parathyroid hormone (PTH), urea, creatinine and albumin level between the intervention group and the standard group of the hemodialysis patients.
b) To evaluate the effectiveness of the SPB on hemodialysis patients' total daily calories, protein and phosphate intake.
c) To evaluate the effectiveness of the of SPB on hemodialysis patients' food satisfaction
d) To evaluate the effectiveness of the of SPB on hemodialysis patients' adherence to PB

1.4 Significant of the Study

This study will be significant endeavor in promoting a simple and user friendly tool for dialysis patients to control their phosphate level. It also will provide an insight to the patient by improving their knowledge and understandings about the phosphate binders with phosphate food contents and phosphate additive in convenient and processed foods. Subsequently, the rate of patients' non-adherence to PB and high dietary phosphate intake from phosphate additive would be reduced with the establishment of the use of SPB.

Besides, the dialysis patients and the dialysis team can easily estimate amount of the food and number of PB should be taken to meet the target phosphate level without referring to the high phosphate food list. Lastly, this intervention will be beneficial to the dialysis team in the management of hyperphosphatemia and reducing the rate of hospitalization due to consequences of hyperphosphatemia.

1.5 Operational Terminology Definition

Hemodialysis referred to a process that duplicate the kidney function for kidney failure patients in reducing the body's waste and excessive fluids. This treatment usually lasts for four hours and is performed three times a week. During this procedure, blood is carried from the patient to a dialyzer (artificial kidney), which is a device comprised of thousands of very fine hollow fibers. These fibers create a semi-permeable membrane and as blood flows through inside the membrane dialysate flows in the opposite direction on the outside, removing impurities and excess water and properly adjusting the chemical balance of the blood. The "clean" blood is then carried back into the patient. During treatment, patients are connected to a dialysis machine and hence their movement is limited. However, they are usually positioned in a comfortable chair and may read, write, and watch television or sleep (Daugirdas, Blake, Peter G., Ing & Todd S., 2015).

Hyperphosphatemia is an abnormal phosphate concentration in the blood. It often happens in renal failure patients especially when there is an excessive taking of phosphate rich food. Average phosphorus levels should be between 0.81 mmol/L to 1.45 mmol/L. It causes the abnormal metabolism of calcium, vitamin D and parathyroid hormone and which subsequently cause mineral and bone disorder and vascular calcification (Cannata-Andia & Rodriguez-Garcia, 2002).

Dietary Phosphate content is referred to the amount of phosphorus which exists in the food. Most of the foods contain phosphorus especially in high protein foods like meat, fish, egg, bean and dairy products. For dialysis patients, they are not allowed to take more than 1000 mg phosphorus daily (Barbara A. Bowman, 2012).

Phosphate binders are the medications used to reduce the phosphate absorption in dialysis patients. It is usually taken with their meals and snacks. It works by binding the phosphate in the gastrointestinal tract and making it unavailable to the body absorption. There are 3 types of phosphate binder: aluminum based, calcium based and aluminum/ calcium free (Bellasi, Kooienga, & Block, 2006).

Food satisfaction is the emotions, feelings and their perception on the food that they are consumed which is related to social, physical or psychological sensation. This information can help to identify the gaps and develop an effective action plan for improving the compliance of dialysis patients to renal diet (Vad Andersen & Hyldig, 2015).

Adherence to phosphate binder referred to how well the patients taking their phosphate binder as prescribed by clinician with the correct dose and recommendation of regimen under limited supervision. There are divided into two categories (unintentional and intentional). Unintentional non adherence is defined as patients prevented from taking the medication due to barriers beyond their control. While the intentional non adherence is the patients decides not to take the PB as recommended due to their own beliefs (Petel, Antoniou, & Popat, 2017).

CHAPTER 2

LITERATURE REVIEW

2.1 Phosphorus in Human Body

Phosphorus is the second most abundant mineral in human body after calcium (Bellasi et al., 2006). It is also an essential element which plays an important role in multiple biological processes in the body. An approximately of 700 g to 875 g phosphorus is present in the adult body of which 85% is in the skeleton (bone and teeth); 14% in the intracellular (soft tissue or blood) and only 1% in the extracellular compartment (Figure 2.1) (Moe, 2006; Uribarri, 2007).

In skeleton, phosphate is primarily complexes with calcium in the form of hydroxyapatite crystals, the remaining phosphate appear as amorphous calcium phosphate (Kooienga, 2007; Penido & Alon, 2012). In intracellular, the phosphorus typically exist mainly as organic compounds as phosphate esters and to a lesser extent as phosphoproteins and free phosphate ions in the soft tissue and cell membranes. Only about 0.001 mmol/L free inorganic phosphate concentration is found in cell (Moe, 2006).

In the extracellular fluid, about 10% of phosphorus content is bound to protein, 75% is complexes to sodium, calcium and magnesium and the remainder (15%) is present as inorganic phosphate (Pi) that is freely circulating and measured (Figure 2.1). Thus, the serum measurement only showed a minor fraction of the total body

phosphorus in the human body. It is not always reflecting well of the total body phosphorus (Heaney, 2012). The following calculations are used to convert between the phosphate concentrations (Johnson, 2010):

• 1 mmol of phosphate = 31 mg of elemental phosphorus

• 1 mmol/L of phosphate = 3.1 mg/dL (or 31 mg/L) or phosphorus

• 1 mg of phosphorus = 0.032 mmol of phosphate

• 1 mg/dL of phosphorus = 0.32 mmol/L of phosphate

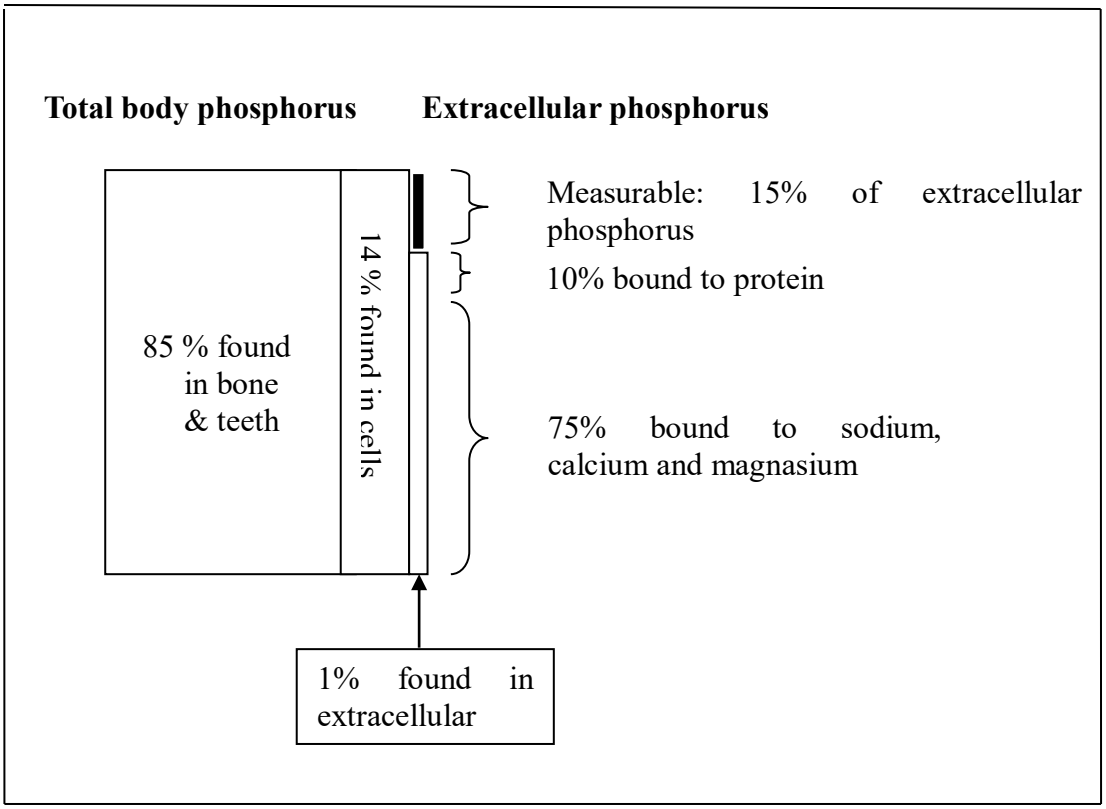

Figure 2.1 Distribution of total body phosphorus (Adapted from Moe, 2006)

Generally, serum phosphate involve with multiple organs and hormones in regulating the phosphate balance (phosphate homeostasis) in human body. In usual phosphate balance, the dietary phosphate intake is balanced by the phosphate

excretion in the urine and feces (Blaine et al., 2014). The normal range of serum phosphate for infant is 1.50 - 2.65 mmol/L and 0.80 - 1.45 mmol/L in adults (Razzaque, 2011; Shaikh, Berndt, & Kumar, 2008).

The intestinal, kidney and bone are the three important organs involve in phosphate homeostasis (Berndt & Kumar, 2009). The main hormones that involve in the regulation of serum phosphate are vitamin D, parathyroid hormone (PTH) and fibroblast growth factor-23 (FGF23) with its cofactor klotho and sodium-phosphate co-transporters (Npt2a,Npt2b,Npt2c) (Barbara A. Bowman, 2012). Others factors that are also involve in regulating the phosphate are diet, time of day, and also the age, gender and genetics (Lederer, 2014).

2.2 Phosphate Homeostasis

For body to maintain the balance of serum phosphate, equilibrium must be established between the amount of phosphate in the plasma and in the extracellular fluid (Uribarri, 2007). The maintenance of phosphate homeostasis is mainly handled by the intestinal, kidney and bone (Lederer, 2014; Moe, 2006). Overall intake and excretion is determined by the net balance of ingested and absorbed phosphate from diet, excretion and reabsorption of phosphate in the urine or feces; in addition of the bone formation and resorption (Berndt, Schiavi, & Kumar, 2005; Robert, Michael & Orson, 2013).

2.2.1 Intestinal Absorption

Phosphorus exists in an organic form in most of the foods. It is usually found in animals or plants protein rich food. It will break down into the inorganic form which can be absorbed by the human body. This inorganic phosphorus (Pi) is absorbed in small intestinal especially in jejunum and ileum through a passive diffusion along with an electrochemical gradient (Bellasi et al., 2006; Uribarri, 2007) and also through active transport across the cells under the influence of the vitamin D ($1\alpha,25(OH)_2\ D_3$) and PTH, using the sodium phosphate co-transporter type 2b (Npt2b) (Penido & Alon, 2012). The passive diffusion is where the inorganic phosphate moves across cell membrane without energy. Its movement is based on the concept of the high concentration to an area with lower concentration.

Generally, the passive diffusion happens rather than the active transport process. The active transport process only happens when the dietary phosphorus intake is low (demands for phosphate are increased) or high (demands for phosphate are decreased) (Russell, 2001). The phosphate moves against the concentration gradient from a lower concentration to higher concentration of the membrane. All this active process needs the Npt2b as a transporter where the Npt2b is regulated by dietary phosphate, vitamin D and PTH (Joanne Marks, Debnam, & Unwin, 2010).

Previous studies revealed that when there was a high phosphorus intake, it induced a decrease of serum $1,25(OH)^2$ D level (vitamin D) that lower the number of Npt2b production, which reduced the absorption of phosphorus in intestinal and balance the serum phosphate concentration in the body (Ferrari, Bonjour, & Rizzoli,

2005; Martin, Ritter, Slatopolsky, & Brown, 2005). On the other hand, when there are low phosphate intake, the serum $1,25(OH)^2$ D level will increase and more phosphate will be absorbed in the intestinal (Ferrari et al., 2005; Martin et al., 2005).

As mention above, only the inorganic form of phosphate can be absorbed by human body. Thus, the dietary phosphate bioavailability of food shows the real proportion of the phosphate that enters into the body to have passive diffusion or active transport effect (Marks, Debnam, & Unwin, 2013; Uribarri, 2007). Normally, there is about 1200 mg/day of phosphorus that we consumed daily but only about average of 720 - 960 mg (60 - 80%) of this dietary phosphate is absorbed by the intestinal (Figure 2.2).

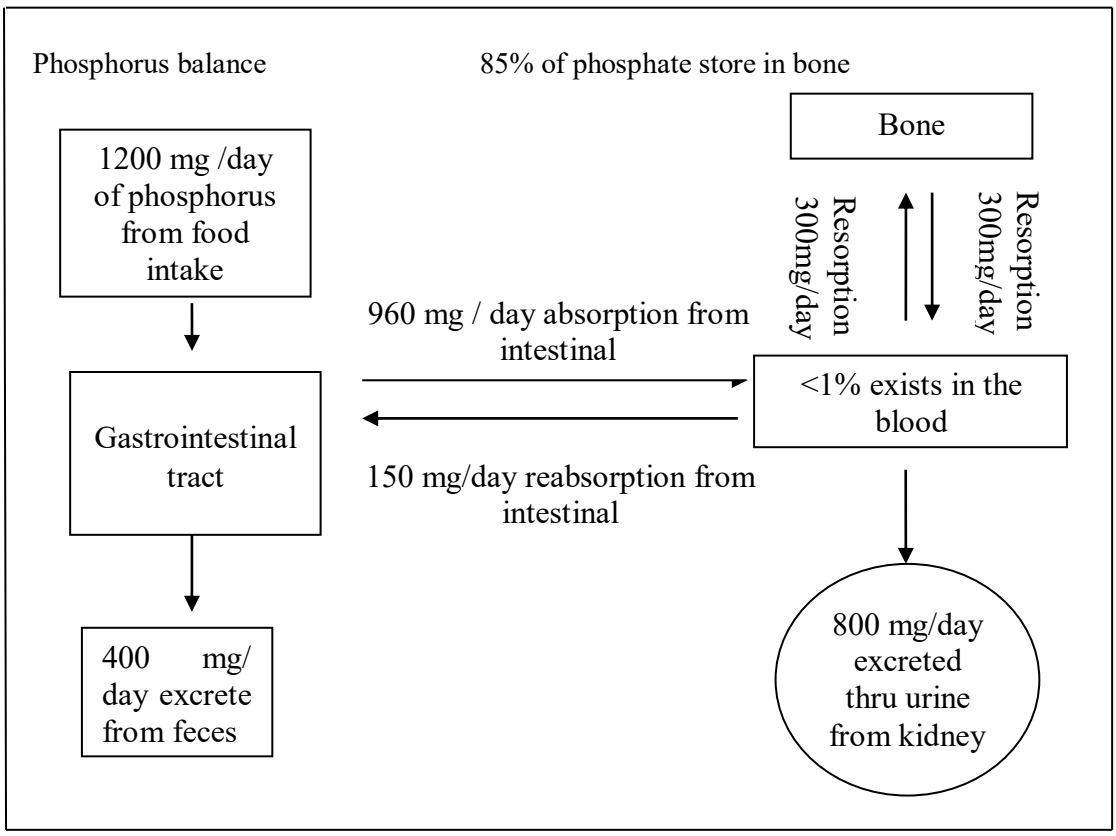

Figure 2.2 Phosphate homeostasis
(Adapted from Hruska, Mathew, Lund, Qiu, & Pratt, 2008)

2.2.2 Kidney Phosphorus Handling

The kidney plays an important role in the phosphate homeostasis. As the phosphate is less bound to albumin or protein, it is easily filtered at the glomerulus of the kidney (Uribarri, 2007). In normal adults, about 3700- 6000 mg/day of phosphorus is filtered by the glomerulus daily. Phosphate is reabsorbed back along the nephron, where 75% of the filtered phosphorus will be reabsorbed by the proximal tubule; 10% by the distal tubule and 15% is lost in urine (Blaine et al., 2014; Uribarri & Calvo, 2003). The 15% of the phosphate that excretes in urine is the total net amount of the absorbed phosphate from the intestinal (Figure 2.2).

The inorganic phosphate (Pi) reabsorption across the proximal tubule and distal tubule is an energy-dependent process that using the sodium phosphate co-transporters as like in the intestinal. The two co-transporters are sodium phosphate co-transporter type 2a and type 2c (Npt2a & Npt2c). Both co-transporters are located in the brush border membrane of the renal tubule cell (Lee & Marks, 2015; Prasad & Bhadauria, 2013). The amount of Pi reabsorption is depends on the dietary phosphate intake or PTH which can change the abundance of these co-transporters in the renal tubule membrane cells (Blaine, Weinman, & Cunningham, 2011).

Therefore, when there is a low phosphate intake there will be an increase number of Npt2a and Npt2c level in the brush border. It gives a result in increasing the Pi absorption from the urine. Whereas, the high phosphate intake decrease of these abundance of co-transporters leads to reduce the phosphate reabsorption and result in a high phosphate in urine (phosphaturia) and more phosphate will be excrete out

from the body (Amatschek, Haller, & Oberbauer, 2010). Generally, the dietary phosphate or PTH can rapidly changes the insertion or removal of the Npt2a (within minutes to hours) and Npt2c (within hours to days) from the brush border of tubule membrane cell to balance the serum phosphate concentration (Blaine et al., 2011; Razzaque, 2011; Reddi, 2014). Thus, the kidney is an important organ in phosphate homeostasis process.

2.2.3 Bone Remodeling

Bone remodeling is a lifelong continuously active process where the old bone is removed from skeleton and the new bone is formed through a matrix mineralization (Seeman, 2009). The process involves two principles cell types: the bone reabsorption (bone breakdown and release calcium and phosphate from the bone tissue to the blood) by osteoclasts and bone deposition (forming new bone tissue) by osteoblasts (Rucci, 2008). When the bone reabsorption is faster than the bone deposition, the bone will becomes more fragile and expose to bone fractures.

There are two main relation of the phosphorus to the bone. Firstly, the inorganic phosphate is one of the two main components that require for hydroxyapatite formation. Eighty five percent of the total body phosphorus are used to form the crystalline hydroxyapatite, $Ca_{10}(PO_4)_6(OH)_2$ in the bone (Nandeesh, 2012). Secondly, the serum phosphate concentration seems to be affecting the osteoblast and osteoclast function by 3 hormones (PTH, calcitonin, and vitamin D) with another 2 target organs which are kidney and GI tract to balance the phosphate concentration in the body (Heaney, 2012).

In brief, the elevated of PTH can increase the number of osteoclasts for bone reabsorption to increase the serum calcium and phosphate while the elevated of vitamin D increase the absorption of calcium and phosphate in the intestinal tracts. When the calcium is high, the PTH will decrease and it will increase the calcitonin to reduce the osteoclast activities (Ahtur & Hall, 2006).

2.3 Phosphorus Homeostasis in Chronic Kidney Disease

Phosphate metabolism disorder is the most common complication in CKD patients. Level of phosphate is usually above the normal range in most of the CKD patients once their GFR is less than 15-30 ml/min (Hruska et al., 2008). The impaired kidney has cause reducing of renal phosphate excretion. It also reduces the calcitriol production when there is insufficient renal mass for 1-α-hydroxylase activity. Besides, it also causes an increase of PTH and FGF 23 (Craver et al., 2007). Figure 2.3 below showed the pathways of the disordered phosphate metabolism.

Generally, the hyperphosphatemia rarely occur in the early stage of CKD; there are only less than 10% of patients in stage 3 CKD show high level of phosphate. Majority of them achieve the normal phosphate level with an abnormal GFR due to the compensation of elevated FGF23 (Martin, David, & Quarles, 2012). Study showed that the FGF23 rises progressively as early as CKD stage 2 to 3. It was produced by osteoblasts in the bone and its concentration rise with a decline of GFR (Lopez et al., 2011).

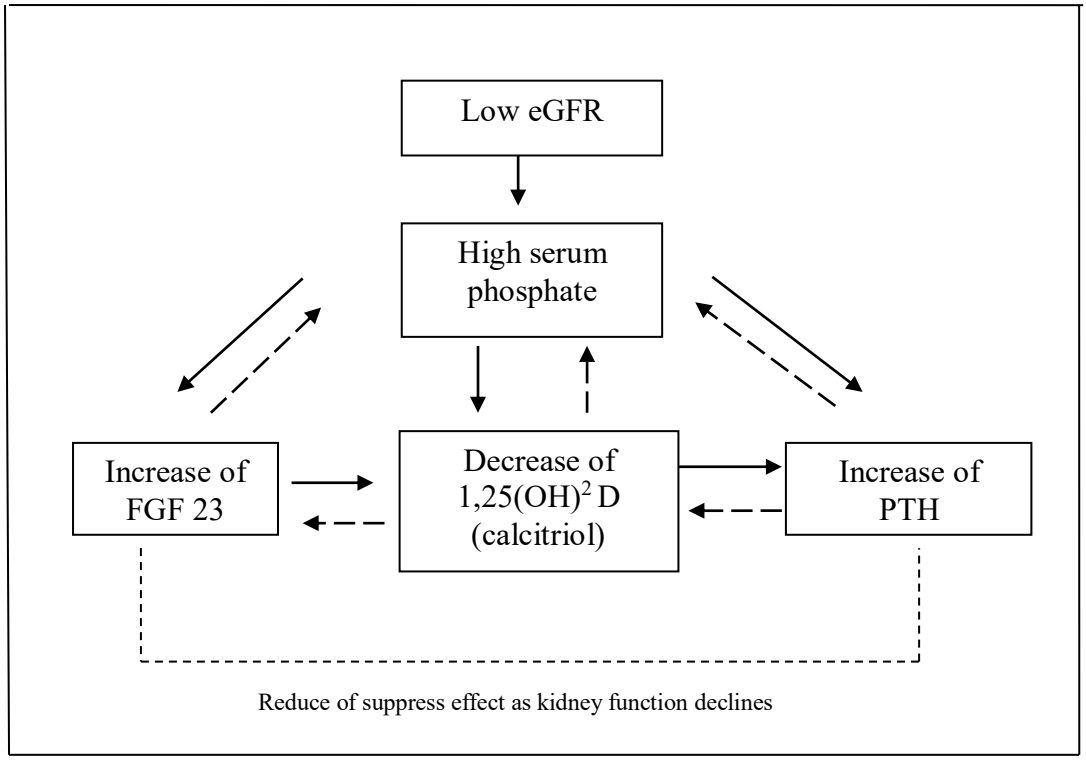

Figure 2.3 Phosphate metabolism disorder in early stage of CKD (dashed lines indicate counter regulatory pathway (Adapted from Kevin J. Martin & González, 2011).

The elevated FGF23 decreases the proximal tubule phosphate reabsorption in the kidney and increased the phosphate excretion in the urine. It also suppresses the calcitriol synthesis and lowering the effect of Npt2b co-transporter to decrease the intestinal phosphate absorption from the diet (Inoue et al., 2005; Shimada et al., 2004). Besides that, the reduction of calcitriol by the FGF23 also led to the reduction of calcium absorption and stimulates the PTH secretion (Cheng, Kuro-o, & Razzaque, 2011; Spiegel & Brady, 2012).

The elevated PTH will then decrease the abundance of Npt2a and Npt2c in renal proximal tubule and further reduce the phosphate renal reabsorption (Hill et al., 2013; Martin, Ritter, Slatopolsky & Brown et al., 2005). Indirectly, it increases the

excretion of phosphate to the urine due to lower renal phosphate reabsorption (Ix, Shlipak, Wassel, & Whooley, 2010). All these compensatory situations attempts to balance the serum phosphate and calcium level in early stage of CKD patients (Oliveira et al., 2010). Hence, it explains why the PTH is elevated as early before hyperphosphatemia is occurred.

There was a study reported high PTH happened in 60% of patients with stage 3 CKD, 70% in stage 4 and 90% in stage 5 but less than 10% of stage 3 CKD have hyperphosphatemia (LaClair et al., 2005). These data had proofed that the elevated FGF23 had combat the rise of the serum phosphate as GFR falls. However, as the GFR continued to decline, the renal phosphate excretion will reach the maximum level leading to persistent hyperphosphatemia. The persistent hyperphosphatemia will further increases of the secretion of PTH. Lastly, the prolonged high PTH leads to secondary hyperparathyroidism (SHPT) (Bergwitz & Jüppner, 2012).

The SHPT with low calcitriol level will then stimulates the bone resorption and cause further increased of serum calcium and phosphate concentration (Lorenz-Depiereux et al., 2006). If the bone remodeling system did not accommodate the increase of serum phosphate concentration, the serum phosphate can interact with calcium and cause calcification in the blood vessel, heart valves, myocardium and others soft tissues which can cause high risk of mortality among these patients (Block et al., 2004; Janigan, Hirsch, Klassen, & MacDonald, 2000; Kestenbaum et al., 2005; Marco et al., 2003; Saliba & El-Haddad, 2009; Young et al., 2005).

In conclusion, the normal serum phosphate level happens in early stage of CKD. There will be net zero balance of serum phosphate even though there is excess of phosphate in CKD patients compare to healthy individuals (Huang & Moe, 2013). With the gradual fall of GFR, the decrease in renal excretion cause positive phosphorus balance which will further stimulates elevated of the PTH and develops SHPT (Bolasco, 2009; Levin et al., 2006). The SHPT can be occurring before the hyperphosphatemia is present. The overt hyperphosphatemia is increase when both FGF23 and PTH are no longer sufficient to maintain the zero phosphate balance (Yamada et al., 2015).

2.4 Consequences of Hyperphosphatemia in CKD

Hyperphosphatemia is a key factors that cause the hyperthyroidism, mineral bone disease (Martin & González, 2011), vascular calcification (Achinger & Ayus, 2006), left ventricular hypertrophy and cardiovascular mortality in CKD patients (Goodman et al., 2000; Hsu & Wu, 2009; Oliveira et al., 2010). There are many studies contested the claim that cardiac disease was the major cause of death in CKD patients (Block, Hulbert-Shearon, Levin, & Port, 1998; Furgeson & Chonchol, 2008; Ganesh, Stack, Levin, Hulbert-Shearon, & Port, 2001; Gutierrez et al., 2008; Henry et al., 2002; Jean et al., 2009).

A study conducted by Block *et al*. was the first study which demonstrated that hyperphosphatemia was the main cause of the mortality and morbidity in hemodialysis patients (Block et al., 1998). The study revealed that 6% higher mortality risk for each of 0.32 mmol/L higher phosphate level. Ganesh *et al.* also

supported the same hypothesis that the hyperphosphatemia and the elevated PTH increased the risk of cardiac death (Ganesh et al., 2001). They found 9% higher risk of death related to coronary artery disease and 6% higher risk in sudden death with only 0.232 mmol/L raised in serum phosphate level in hemodialysis patients.

A more recent meta-analysis on 14 studies and 109,670 CKD patients had further supported the evidence of the association between the hyperphosphatemia and the mortality in CKD (Palmer et al., 2011). The authors systematically reviewed the data from all the cohort studies which had adjusted for confounding factors like age, sex, diabetes, kidney function and also duration of dialysis in all-cause mortality. The authors demonstrated that the increase of 0.32 mmol/L in phosphate level caused the increase risk of mortality by 18%.

Besides that, there were some studies which were looking at the calcification risk in the pre-dialysis CKD patients as well (Anand, Lahiri, Lim, Hopkins, & Corder, 2006; Kramer, Toto, Peshock, Cooper, & Victor, 2005; Moe & Chen, 2004; Toussaint, Lau, Strauss, Polkinghorne, & Kerr, 2008). A study by Tomiyama *et al.* demonstrated that the hyperphosphatemia can cause the endothelial dysfunction (thickening or hardening the vessels) in CKD patients even only in stage 2 to 4 (Tomiyama et al., 2006). The study revealed that the endothelial dysfunction actually would also bring to greater risk of renal function decline among these patients.

The endothelial dysfunction was one of the causes of atherosclerosis and cardiovascular disease (Di Marco et al., 2008; Shuto et al., 2009). The high phosphate level on endothelial cells inhibited the nitrogen oxide production by

increasing the reactive oxygen species production and inactive the endothelial nitrogen oxide synthase (Takeda et al., 2006). These oxidative stress and reduction of nitrogen oxide production further caused the endothelium dependent vasodilation impairment in the cardiac and cause atherosclerosis and cardiovascular disease (Di Marco et al., 2008; Oliveira et al., 2010; Shuto et al., 2009). One of these studies also highlighted that the endothelium function depletion might also extend to the glomerular endothelium in the kidney and brought to the progression of kidney failure in these patients (Oliveira et al., 2010).

With all the support from these researches, treating the phosphate earlier even before hyperphosphatemia occurs in CKD stage 2 to 4 patients might bring clinical benefits and it may help to reduce the early clinical consequences of mineral bone disease, endothelial dysfunction and later the vascular calcification. It also might slow down the progression of renal failure. There are a few studies which propose to initial phosphate control at earlier stages when phosphate retention had begun, as shown by elevations in PTH and FGF23 levels, but before the hyperphosphatemia occurs (Gutiérrez & Wolf, 2010; Martin & Gonzalez, 2011; Oliveira et al., 2010). The studies attempted to show that early phosphate control may help in reducing the early mineral and bone disturbance. However, in current clinical practice even in Malaysia, the phosphate control are emphasized in ESRD patients who already having hyperphosphatemia after dialysis.

Many epidemiology studies had highlighted that majority of the dialysis patients had high phosphate level (Eiji Takeda, 2011). Data from the International Dialysis and Practice Pattern Study (DOPPS) revealed that less than 50% of the dialysis

patients meet the target phosphate level (Young et al., 2000). While in the Malaysia, there was only 15% of dialysis patients meet the target phosphate level recommended by KDIGO (0.80 to 1.45mmol/L) and 42% of the hemodialysis patients had phosphate level more than 1.8mmol/L in 2012 (Kok et al., 2013).

In conclusion, hyperphosphatemia is independent risk factors for endothelial dysfunction that cause progression in renal failure and cardiovascular mortality CKD. Normalization of phosphate level is urging for reducing these fatal consequences as early as at stage 2-4 CKD. However, the evidence for controlling the phosphate in early stage of CKD is currently still insufficient to inform clinical decision making policy or practice guidelines. Thus, more investigations should be carried out to assess the significance of early control of phosphate level even in the stage 2 to 4 CKD patients for better management of hyperphosphatemia.

2.5 Management of Hyperphosphatemia

In clinical practice, the management of hyperphosphatemia is by controlling the intake and removal of phosphate from the body. There are 3 main strategies for controlling the hyperphosphatemia:

a) Removal of phosphate from adequate dialysis
b) Phosphate binders for minimize the intestinal absorption
c) Restriction of dietary phosphate intake