Evaluation of phosphate knowledge and the effectiveness of a phosphate management protocol to achieve optimum serum phosphate levels in haemodialysis patients

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Abstract

Despite current medical and dietetic treatments designed to achieve and maintain acceptable serum phosphate levels, current prevalence rates of hyperphosphataemia and associated health risks, in haemodialysis patients indicate that controlling serum phosphate levels remains a challenge in the 21st century.

The aims of this study were to evaluate (1) the effectiveness of a phosphate management protocol designed to optimise serum phosphate levels in patients undergoing regular haemodialysis and (2) changes in phosphate knowledge scores as a result of phosphate education by a renal research pharmacist and renal dietitian.

A randomised, controlled trial was carried out at haemodialysis units at Barts and the London NHS Trusts and satellite units. The project followed thirty-four clinically stable adults undergoing regular haemodialysis with a serum phosphate level > 1.8mmol/l on at least one occasion within 4 months of starting the study..

Intervention entailed management of serum phosphate levels using a specially designed protocol during a 4 month study period implemented by a renal dietitian and renal pharmacist, in contrast with standard practice. The protocol group for this study received phosphate education from the renal pharmacists and renal dietitians, as part of the protocol procedure, whereas the control group received instruction from a renal doctor and another renal dietitian. Changes in serum phosphate levels were monitored over period of 4 months in both groups. Before and 4 months after the study, patients' phosphate knowledge was also tested in both groups using a phosphate knowledge questionnaire specially designed for this study.

The results showed that on comparing the phosphate management protocol group and patients receiving standard practice a significant difference in the mean change in serum phosphate levels was achieved (-0.22 ± 0.67mmol/l, t= -1.23 vs +0.19 ± 0.32mmol/l, t= +2.46, P = 0.03).

However, there were no detectable differences in patients' knowledge about complications of hyperphosphataemia pre and post intervention in either group, indicating a need to address this issue.

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This thesis is dedicated to my late father Lloyd Yokum, who is greatly missed.

Chapter 1: INTRODUCTION

1.1 Background

Disorders of mineral metabolism, which include hyperphosphataemia, hypocalcaemia and secondary hyperparathyroidism, are independently associated with morbidity and mortality in the haemodialysis population (Block et al., 2004). All of these conditions can be treated by using dietary phosphate restriction, medication and haemodialysis. However the prevalence rates reported in the literature indicate that these disorders remain a challenge in renal units in the developed world (Hecking et al., 2004). To address these issues evidence-based clinical guidelines, which include targets for serum biochemistry, have been developed (National Kidney Foundation 2004, The Renal Association 2007).

Technological advances in haemodialysis have already demonstrated that hyperphosphataemia could be eradicated if all of the haemodialysis patients were able to be dialysed daily i.e. nocturnal haemodialysis (Kuhlmann 2007). Unfortunately the reality is that in the first decade of the 21st century health services, with their limited finances and resources, are trying to control serum phosphate levels using conventional haemodialysis which is usually three 4-hour sessions per week. Since phosphate management clinical guidelines have been published, members of renal multi-professional teams have been conducting original research in their specific renal clinical areas with the aim to help their patients achieve these targets for serum biochemistry. The ultimate goal is to observe a reduction in morbidity and mortality rates in haemodialysis populations worldwide.

This thesis considers how serum biochemistry can be optimised with specific reference to phosphate management. In order to provide an introduction to this renal physiology, historical background and current perspectives of kidney disease and its treatments are briefly considered.

1.2 Literature Review

This chapter also contains a review of the literature which relates to the research previously undertaken to determine the effectiveness of phosphate management education to improve serum phosphate levels, adherence to phosphate binder medications, phosphate knowledge of haemodialysis patients regarding medical complications and phosphate management treatments. Articles published on the use of phosphate management clinical protocols and algorithms, were also searched. Information on questionnaire design was investigated, in relation to questionnaire content validity and testing reliability.

1.2.1 Search strategy

The databases Medline (1950 to date), Embase (1974 to date), CINAHL (1982 to date), Allied and complementary medicine (1985 to date), DH-DATA (1983 to date), King's Fund (1979 to date), PsycINFO (1806 to date) were used to search for relevant published articles. Medical subject headings (MESH) were used to ensure a comprehensive literature search was achieved. The Boolean operator "AND" / "OR" was used to combine the search to find articles using all of the terms for example hyperphosphataemia, haemodialysis / hemodialysis, outpatients, patient education, patient compliance, multidisciplinary team, questionnaires, knowledge, validity, reproducibility, reliability, clinical protocols and algorithms.

Paediatric or animal research articles were excluded.

1.3 Renal Physiology

This section provides an overview of renal physiology in health and chronic kidney disease (Drüeke et al., 2003, Kriz et al., 2003).

The kidney is comprised of complex anatomical structures that enable it to carry out the physiological processes needed to maintain, via the bloodstream, a stable internal environment which is essential for the normal functions of all cells in the body. Renal function controls water and salt balance by regulating the excretion of water, sodium, potassium, chloride, phosphate, calcium, magnesium and many other substances.

1.3.1 Structure of the healthy kidney

The kidneys are located behind the peritoneum at the back of the abdominal cavity and extend from the twelfth thoracic vertebra to the third lumbar vertebra. Each kidney is covered by a fibrous capsule. The renal cortex is the outer section of the kidney and the renal medulla is the inner section which contains the renal pyramids. Each kidney consists of seven lobes, each containing a renal pyramid which converges at the pelvis of the kidney to form both minor and major calyces at the upper end of the ureter into which urine passes from the pyramids (O'Callaghan 2006). A cross-sectional view of the kidney's structure is shown in Figure 1.1.

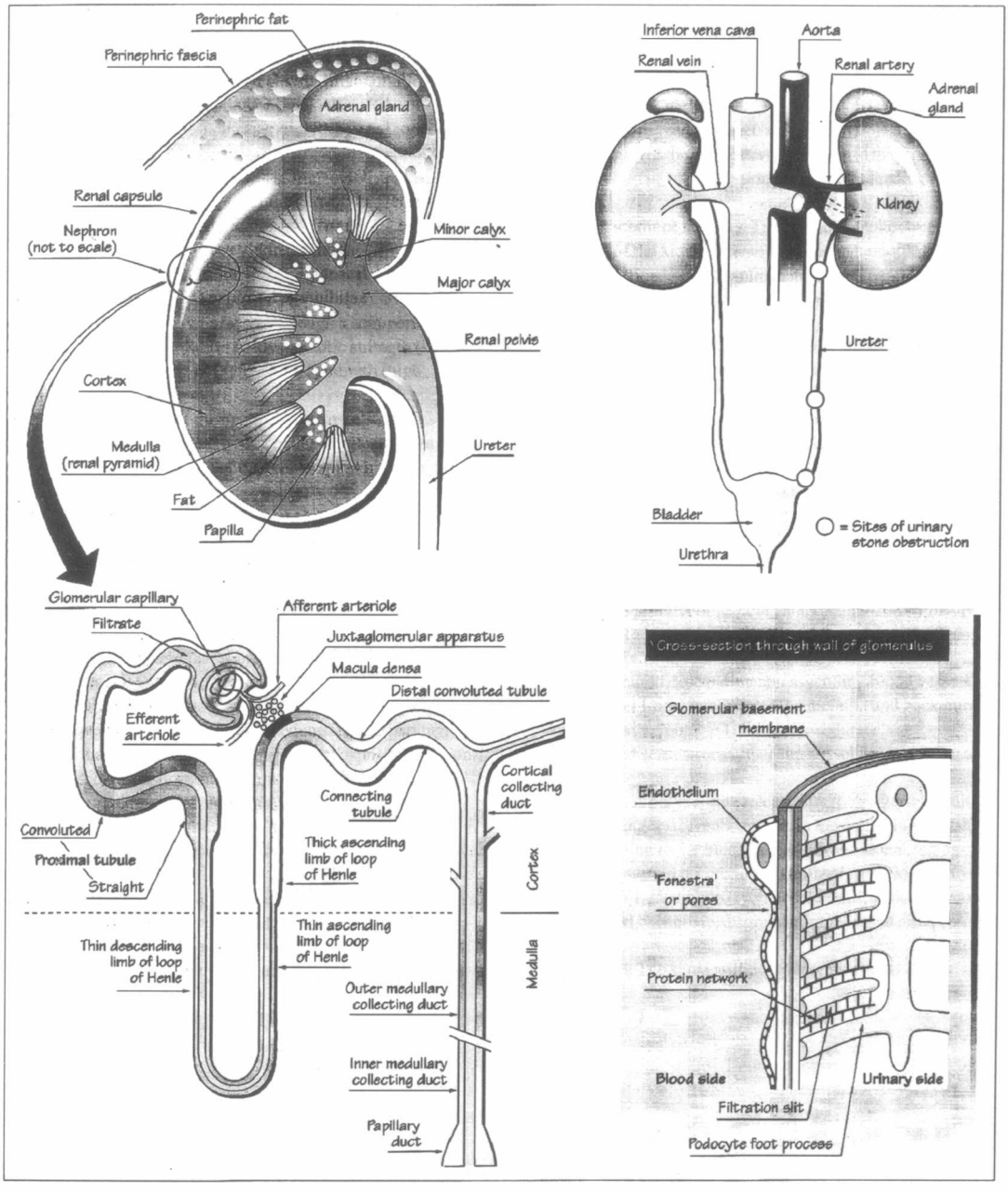


Figure 1.1 Diagrams illustrating the chief features of kidney anatomy and microstructure. (O'Callaghan 2006)

The nephron is the basic unit of the kidney. Each kidney contains approximately 400,000 – 800,000 nephrons, but this number decreases with age. Each nephron consists of a renal corpuscle, proximal convoluted and straight tubules, loop of Henle and a distal convoluted tubule connected to the collecting duct. The cortex contains all of the renal corpuscles and convoluted tubules while the medulla contains the loops of Henle and the final portions of the collecting ducts (O'Callaghan 2006). A cross-sectional view of the nephron's structure is shown in Figure 1.1 (bottom left).

1.3.2 Brief overview of the production of urine

Glomerular filtrate production

The renal corpuscle consists of a glomerulus which is a complex network of capillaries and associated cellular structures, and a surrounding cup-like epithelial sheath, the Bowman's capsule. Blood flows into the glomerular capillaries via an afferent arteriole and exits via an efferent arteriole. A high hydrostatic pressure is created by vasoconstriction of the efferent arteriole which forces water, substances, including small molecules, through a filtration barrier to produce glomerular filtrate, collecting in the Bowman's capsule (O'Callaghan 2006).

The filtration barrier consists of three layers, two of them cellular layers and between them an extracellular basement membrane. The first cellular layer is the thin endothelium lining the glomerular capillaries. This has numerous pores, it is a fenestrated endothelium which allow the passage of water and molecules but not blood cells. The next layer is the glomerular basement membrane composed of Type IV collagen, laminin and various negatively charged proteoglycans. The third layer consisting of branched epithelial cells (podocytes), which extend foot-like processes, inserted into the surface of the glomerular basement membrane. The foot processes originating from different podocytes juxtapose each other, the narrow spaces between them forming filtration slits (slit pores) covered by a dense layer (the slit diaphragm). In healthy kidneys, the glomerular membrane prevents the passage of larger molecules from glomerular capillaries but allows water, ions and small molecules to pass into the filtrate (O'Callaghan 2006). A diagramatic view of the glomerulus wall is shown in Figure 1.1.

The production of glomerular filtrate normally occurs at a rate of 125ml/min/1.73m^2 and collects in the Bowman's capsule before draining into the tubules where both its volume and content are altered by reabsorption and secretion. The different structures comprising the remainder of the nephron are lined by simple epithelial cells which regulate the filtrate contents.

Most reabsorption occurs in the proximal tubules and the final adjustments to the urine composition occur in the distal tubules and the collecting ducts. The function of the loops of Henle is to concentrate the filtrate which then passes via the distal convoluted tubule and collecting ducts as urine to the ureter and then by peristaltic action to the bladder where it accumulates. Under the control of the nervous system, the contraction of muscles in the bladder walls and relaxation of sphincter muscles around the bladder urethral opening of the bladder allow urine to be excreted from the body (Kriz et al., 2003).

Transport systems in the kidney

Both active and passive transport are involved in moving substances between the blood and the filtrate in the production of urine in healthy kidneys. Active transport involves the movement of substances across cellular membranes by molecular pumps which expend energy during the process. Passive transport is the process by which solutes and water move by diffusion down concentration gradients.

1.3.3 Normal regulation of serum phosphate and calcium levels

The hormonal functions of the kidney

These include the following:-

i) Intact parathyroid hormone (iPTH) is produced by the parathyroid glands which acts directly on the kidney and has an important role in calcium and phosphate regulation. The functions of iPTH will be explained later in this section.

ii) Vitamin D, calciferol, is a steroid hormone, produced within healthy kidneys, which has an important role in calcium and phosphate regulation. Vitamin D_3, cholecalciferol, is produced in human skin from 7-dehydrocholesterol, under the action of ultra-violet light. Dietary calciferol from animal and plant sources is absorbed into the bloodstream by the small intestine. The liver converts cholecalciferol into 25-hydroxycholecalciferol which is then transferred to the proximal tubule cells in the kidney. At this location the 25-hydroxycholecalciferol undergoes a second hydroxylation to 1,25-dihydroxycholecalciferol ($1,25(OH)_2$ (calcitriol), which is known as the active form of vitamin D (Altmann 2002). The functions of $1,25(OH)_2$ vitamin D_3, will be explained later in this section.

The homeostatic functions of the kidneys

In health, the normal ranges for serum calcium and phosphate are 2.2 – 2.6 mmol/l and 0.8 - 1.5 mmol/l respectively. These levels are achieved and maintained homeostatically by processes including the actions of iPTH and $1,25(OH)_2$ vitamin D_3 (Drüeke et al., 2003). These will now be discussed in detail.

Serum calcium homeostasis

Calcium homeostasis is dependent on the parathyroid glands, the gastro-intestinal (GI) tract, bones, the kidneys and the transport of calcium in the serum (Altmann 2001). The majority of calcium, in the body, is stored in the bones (99%) whereas the remaining calcium is found in the extracellular fluid (serum) and intracellular fluid. Calcium in the blood is either bound to protein (45%) or available for ultrafiltration (55%) (Drüeke et al.,

2003). The main function of iPTH is to maintain normal serum calcium levels. The parathyroid gland is stimulated, in response to a fall in serum calcium levels to release more iPTH into the blood. Figure 1.2 illustrates the processes involved in serum calcium homeostasis.

The mechanisms involved in serum calcium homeostasis are very complex in nature. In this section a brief explanation will be provided. The daily calcium intake is approximately 600 - 1350mg in the western diet (Drüeke et al., 2003). On average, this is equivalent to 1000mg of dietary calcium per day. Approximately 40% of dietary calcium is absorbed in the GI tract which is equivalent to 400mg of calcium (Altmann 2001, Drüeke et al., 2003). The kidneys provides the immediate response to maintain serum calcium homeostasis in the short-term whereas the skeleton and the intestines play major roles in maintaining normal range serum calcium levels in the longer term (Drüeke et al., 2003). Due to the active transport systems in the proximal and distal convoluted tubules plus passive transport in the thick ascending of the loop of Henle, the majority of the filtered calcium is reabsorbed, back into the blood. This results in 160mg of calcium being excreted in the urine daily. The active transport in the distal tubules are directly regulated by iPTH and $1,25(OH)_2$ vitamin D_3. Both hormones increase calcium reabsorption at this site in the kidney when hypocalcaemia occurs (Altmann 2001) (Figure 1.2).

Intact PTH plays an indirect role by increasing the activity of 1-α-hydroxylase, the enzyme required for the conversion of 25-hydroxycholecalciferol to $1,25(OH)_2$ vitamin D_3, which occurs in healthy kidneys. This results in an increased synthesis of $1,25(OH)_2$ vitamin D_3 which increases calcium absorption in the GI tract (Altmann 2002, Drüeke et al., 2003).

The transfer of calcium from and to bones is the final mechanism in calcium homeostasis. Intact PTH acts directly on bones where it stimulates bone cells, called osteoclasts, which results in bone resorption, thereby releasing calcium into the blood (Drüeke et al., 2003) (Figure 1.2). Once the serum calcium level rises and achieves a level within the normal range the parathyroid gland is no longer overstimulated and the secretion of iPTH is reduced. This is as a result of negative feedback systems exerted by the serum calcium level and $1,25(OH)_2$ vitamin D_3 (Altmann 2002).

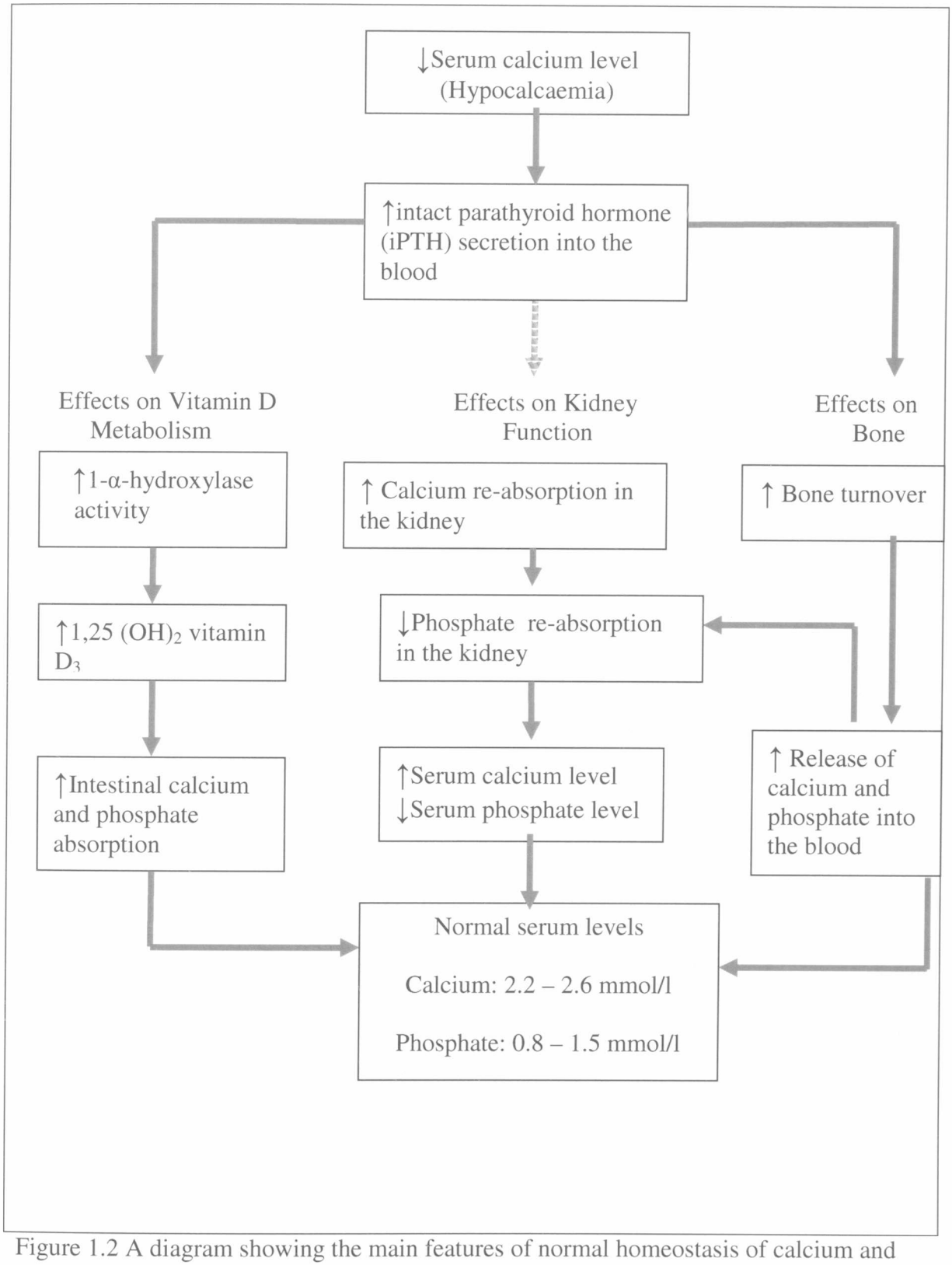


Figure 1.2 A diagram showing the main features of normal homeostasis of calcium and phosphate metabolism (Based on a diagram from: Drüeke TB et al., 2003)

Serum phosphate homeostasis

The distribution of phosphate in the body is: bone (85%), soft tissue (14%), teeth (0.5%), interstitial fluid (0.05%), red blood cells (0.03%) and serum (0.02%) (Pohlmeier et al., 2001). Various metabolic processes within cells require phosphate to activate many enzymes, control active transport across membranes, enable muscular processes etc. Intact PTH, $1,25(OH)_2$ vitamin D_3 and healthy kidneys all have important roles in phosphate homeostasis (Drüeke et al., 2003).

The daily phosphate intake ranges from 775 - 2015mg in the western diet (Drüeke et al., 2003, Kuhlmann 2007). This equates to an average intake of 1400mg of phosphate per day. The proportion of dietary phosphate that is absorbed into the blood, via the GI tract is 70%, which is equivalent to approximately 1000mg of phosphate. Phosphate is actively transported across the intestinal wall. This process can be stimulated by $1,25(OH)_2$ vitamin D_3 (Figure 1.2).

In the presence of an increased serum iPTH level and increased synthesis of $1,25(OH)_2$ vitamin D_3 this results in an increased amount of dietary phosphate being absorbed in the GI tract and an accumulation of phosphate in the blood. However the action of iPTH, in healthy kidneys results in a reduced amount of phosphate being reabsorbed in the proximal tubules, thereby increasing the excretion of excess phosphate in urine. This action of iPTH helps to maintain the serum phosphate level within normal levels (Altmann 2001) (Figure 1.2).

The transfer of phosphate from and to bones also occurs in phosphate homeostasis. The iPTH acts directly on bones where it stimulates osteoclasts to cause bone resorption, thereby releasing phosphate into the blood. However, at the same time phosphate is being deposited in bones by osteoblasts under the action of calcitonin thereby enabling bone to help achieve and maintain a neutral phosphate balance in healthy adults. This dynamic process is known as bone turnover (Altmann 2001, Drüeke et al., 2003).

1.3.4 Altered homeostasis in chronic kidney disease

In this section, the effect that chronic kidney disease (CKD) has on the regulation of phosphate and calcium levels will be explained.

Development of hyperphosphataemia

One of the main characteristics of CKD is the reduced glomerular filtration rate (GFR) caused by damage to glomerular function. This causes less phosphate to be filtered in the kidneys and therefore an accumulation of phosphate in the blood which then directly stimulates the parathyroid gland to produce more iPTH. Initially, normal serum phosphate levels are maintained due to the action of iPTH on the renal proximal tubule to reduce the rate of phosphate reabsorption (Altmann 2001). This compensation mechanism of iPTH is effective until the GFR declines to less than 20ml/min/1.73m^2 (Altmann 2001), equating to CKD stage 4 in current medical terminology (National Kidney Foundation 2004). At this point a rise in serum phosphate levels occurs, which is known as hyperphosphataemia (Figure 1.3). Table 1.1 summarises the stages of CKD and their corresponding GFR.

Table 1.1 Classification of chronic kidney disease stages
(National Kidney Foundation 2004)

Stage	Description	Glomerular Filtration Rate GFR (ml/min/1.73m^2)
1	Kidney damage with normal or ↑GFR	≥ 90
2	Kidney damage with mild ↓ GFR	60 - 89
3	Moderate ↓GFR	30 - 59
4	Severe ↓GFR	15 - 29
5	Chronic kidney failure	<15 (or dialysis)

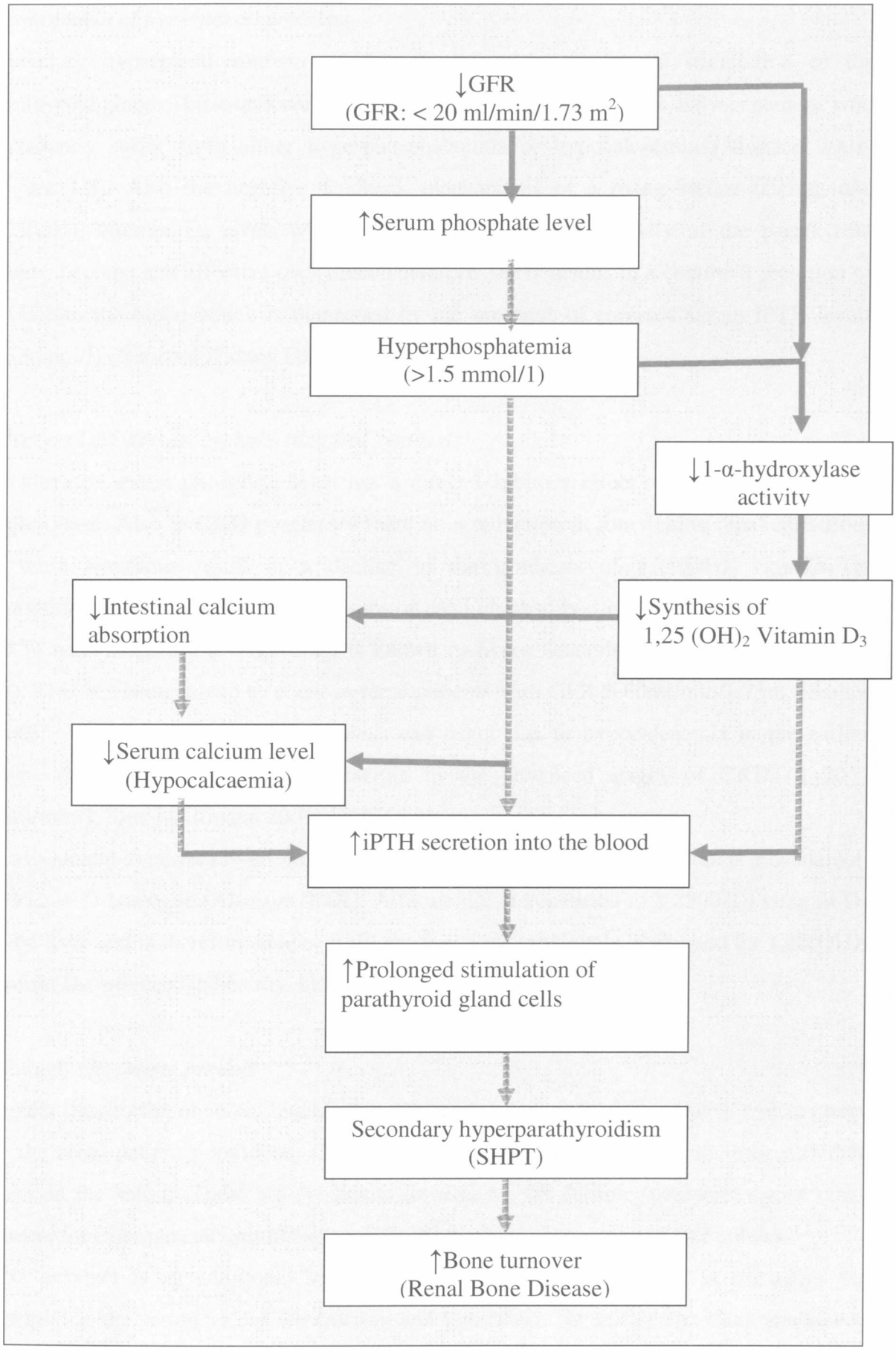


Figure 1.3 Phosphate - calcium homeostasis and advanced kidney disease

Development of hyperparathyroidism

Secondary hyperparathyroidism (SHPT) is defined as prolonged stimulation of the parathyroid gland. This can occur in patients with advanced CKD and dialysis patients who persistently suffer from either hyperphosphataemia or hypocalcaemia (Altmann 2001) (Figure 1.3). Also the negative feedback mechanisms of a rising serum calcium and $1,25(OH)_2$ vitamin D_3 levels which normally suppress the activity of the parathyroid glands, become less effective over time. Therefore SHPT results in a continual secretion of iPTH into the blood which is diagnosed by the presence of elevated serum iPTH levels (>33pmol/l) (National Kidney Foundation 2004).

Effect on 1,25 dihydroxycholecalciferol synthesis

An elevated serum phosphate level has a direct inhibitory effect on the activity of 1-α-hydroxylase. Also as CKD progresses there is a reduction in functioning renal cells Both of these situations result in a decline in the synthesis of $1,25(OH)_2$ vitamin D_3. Consequently, a reduction in the amount of calcium absorbed in the GI tract produces a fall in serum calcium levels, which is known as hypocalcaemia (Altmann 2001) (Figure 1.3). This has been shown to occur in renal patients with GFR ≤ 60ml/min/1.73m^2 (Sadler 2000). Therefore, elevated iPTH levels can occur due to hypocalcaemia in the earlier stages of CKD and hyperphosphataemia in the advanced stages of CKD (≤ 20 - 25ml/min/1.73m^2) (Altmann 2001) (Table 1.1).

The treatment to correct hypocalcaemia and secondary hyperparathyroidism is alfacalcidol, a vitamin D analogue (Altmann 2002). Alfacalcidol is converted to $1,25(OH)_2$ vitamin D_3 in the liver and is therefore able to fulfil the functions previously performed by $1,25(OH)_2$ vitamin D_3, produced in healthy kidneys (Altmann 2002).

Calcium- phosphate product

Regular monitoring of serum biochemistry is an important part of the medical management for the renal patient population. Calcium and phosphate can be found in three different forms in the serum. These are (1) bound to proteins, (2) forming complexes with other solutes, for example calcium-phosphate (CaxP) product, (3) existing as free solutes

CaxP product is an additional serum variable that is monitored. It is calculated by multiplying the serum values for calcium and phosphate. In health, the CaxP product is normally maintained within the range 3.6 – 4.0mmol^{2}l^2 (Altmann 2001). The significance of CaxP product relates to calcium and phosphate forming harmful deposits in soft tissues

in various parts of the body when CaxP product >4.44 $mmol^2l^2$ (National Kidney Foundation 2004). This will be discussed further in section 1.6.3.

The transition from healthy kidney function to advanced CKD without treatment will result in death. Haemodialysis is one type of renal replacement therapy available to renal patients. This treatment will now be explained since all of the patients who participated in the main study were receiving this treatment.

1.4 Haemodialysis

1.4.1 Definition

Haemodialysis is a process whereby the blood is transported from the patient's body and passes through a dialyser, the main component of a haemodialysis machine, where the toxic substances and water are removed. Blood is accessed via a man-made arteriovenous fistula, which is an artery and a vein joined together to form a large blood vessel, or a dialysis line one end of this is located in the patients' heart. Both types of haemodialysis access can withstand fast blood flows.

The dialyser, contains a liquid called dialysate and a semi-permeable membrane containing minute pores. The haemodialysis machine contains components which enable the blood to be mechanically drawn into and through the dialyser at high blood flow rates of 200 - 300ml/min, whereas the dialysate flow is 500ml/min (Pohlmeier et al., 2001). The blood and dialysate are separated by the semi-permeable membrane and flow in opposite directions, at different rates, to achieve optimal removal of small molecules during haemodialysis (Thomas 2003).

1.4.2 Kinetics of haemodialysis

During haemodialysis, the removal of substances from the blood depends on their molecular size. Therefore substances are classified as small, middle or large molecules (Daugirdas 2001, Penne et al., 2005). For example, urea and phosphate are small molecules and uraemic toxins, however their removal from the blood during haemodialysis follow different kinetic principles (Pohlmeier et al., 2001). Urea is synthesised in the liver and is the main nitrogenous waste product excreted by the body (Daugirdas 1993). Urea molecules are able to cross cell membranes easily which results in good urea clearance from the blood into dialysate (Kuhlmann 2007). Phosphate removal is more complicated and will be explained in detail in the next section.

For conventional haemodialysis, which is usually three 4-hour sessions per week, small molecules including water, can easily pass from the blood through the dialyser membrane

pores into the dialysate by diffusion which is driven by a concentration gradient (Daugirdas 2001, Thomas 2003). The middle and large molecules are transported through the dialyser membrane into the dialysate, by convection, or solvent drag, along with water molecules (Daugirdas 2001, Thomas 2003). This mechanism requires water molecules to be forced through the membrane pores by an osmotic or hydrostatic pressure (ultrafiltration). The removal of larger molecules is limited by amount of water the haemodialysis machine is programmed to remove during each haemodialysis session. (Daugirdas 2001, Thomas 2003).

1.4.3 Phosphate removal during haemodialysis

Pohlmeier et al (2001) and Kuhlmann (2007) both describe the kinetics of phosphate removal from the body, by haemodialysis. The distribution of phosphate in the body, which has been discussed in section 1.3.3, is significant with respect to this process.

The phosphate which is freely available in the blood is transferred into the dialysate by diffusion, during the initial phase of haemodialysis which lasts approximately 1 – 2.5 hours. For the remainder of the haemodialysis session, phosphate removal slows down and plateaus (Kuhlmann 2007). The amount of phosphate removed, from the blood, during a standard 4-hour conventional haemodialysis has been quoted as ranging from 600 - 1200 mg (Pohlmeier et al., 2001, Altmann 2002, Kuhlmann 2007). Since only 110mg (0.02%) of the total amount of phosphate in the body is found in the blood, this indicates that additional phosphate located in the interstitial and intracellular body compartments must also be available for removal from the body. The differences in phosphate concentration in different body compartments have led researchers to conclude that the cell membranes are very impermeable to phosphate molecules. Therefore, it is the properties of the cell membranes that have resulted in the slow transfer of phosphate molecules between the intracellular compartment and the blood. This process also continues for a few hours after the haemodialysis session is complete (Pohlmeier et al., 2001).

In summary

The removal of phosphate molecules during haemodialysis is limited due to the fact that the majority of phosphate is located within human body cells. Therefore the transfer of phosphate molecules across cellular membranes and into the blood has been identified as the rate-limiting step in phosphate removal during haemodialysis.

In sections 1.1 – 1.3 of this chapter, background information regarding the aetiology of hyperphosphataemia and its associated complications has been explained. A description of haemodialysis, the life saving treatment, has been given at this stage to illustrate the similarities and differences in the kinetics of phosphate removal by healthy kidneys and haemodialysis machine. Before discussing the challenges of optimizing serum phosphate levels and explaining the rationale for this thesis it would be useful to reflect on historical aspects of renal medicine historical facts which have led to the phosphate management treatments as they are known today.

1.5 Historical Perspective

1.5.1 The development of medical knowledge in relation to kidney function

The physiology of the kidney in health, previously discussed in detail in section 1.3, linked the structures and functions of the kidney with the production and excretion of urine. Early references to urine were described by Hippocrates in the 5th century BC. It is clear from his descriptions that urine was a diagnostic tool (Grant 2000).

Relating urine to health

Galen, a respected Greek doctor who may have served the Roman elite (c AD 129-200) believed that the balance of good health was based around four "humours", blood, phlegm, black bile and yellow bile. The origin, maintenance and movement of blood were associated with the liver and veins, whereas for yellow bile the association was with the bladder and the area around the liver (Grant 2000). It is reasonable to assume that the yellow bile Galen refers to is an early reference to urine stored in the bladder. However, although ancient physicians clearly recognised the problems associated with renal stones and the relevance of examining urine, they did not have a clear perspective about the abnormalities associated with CKD.

The progress of renal medicine

It was not until the 19th century that clinical research began to flourish. This enabled clinicians at this time to carry out post mortems which subsequently helped them establish clinical diagnoses based on their patients' symptoms. Between the years 1820–1842, a doctor named Richard Bright worked at Guy's Hospital, London and his research focused on diseases of the kidneys (Eknoyan 2004). Much later, between 1930 and 1950, Fuller Albright at Massachustts General Hospital, Boston conducted calcium and phosphate

balance studies on patients with conditions affecting their parathyroid gland. He concluded that the primary function of iPTH was to enhance the renal excretion of phosphate since this response was observed before the increased mobilisation of calcium from bone (Felsenfeld et al., 1999).

1.5.2 Hyperphosphataemia

Work published in the late 1960s to 1980s advanced medical knowledge relating to hyperphosphataemia. In 1973, Slatopolsky conducted a study, to investigate hyperphosphataemia, using ureamic dogs. He found that hypocalcaemia and phosphate retention resulted in an overstimulation of the parathyroid glands to produce iPTH (Slatopolsky et al., 1973). Hyperphosphataemia was identified as a clinical problem which occurred when the GFR ≤20ml/min/1.73m^2 (Anon 1978). This meant hyperphosphataemia occurred prior to patients requiring haemodialysis. Also it was found to be directly associated with kidney damage due to the presence of calcium and phosphate deposits in these organs. This was a significant finding as it meant hyperphosphataemia was directly associated with the progression of kidney disease. Such deposits were also found in other parts of the body including blood vessels, myocardium and corneas (Anon 1978). Calcium and phosphate deposits will be discussed in more detail in section 1.6.3.

Other complications associated with hyperphosphataemia mentioned in the literature were renal bone disease and metastatic calcification (Anon 1978). These complications will also be discussed in section 1.6.3.

By the end of the 20th century further evidence emerged, which included statistical analysis to show that hyperphosphataemia was directly associated with mortality in the haemodialysis population (Block et al., 1998). Mortality rates are described in more detail in section 1.6.4.

From this history it can be seen that the knowledge obtained from the studies conducted mainly in the last century led to the development of the treatments for phosphate management. These will now be discussed.

1.5.3 Historical management of hyperphosphataemia

Renal nutrition

Early references to the use of nutrition to treat disease are ascribed to Scribonius Largus at the time of Emperor Claudius (AD 41-54). It is clear from his descriptions that he preferred diet as a therapy rather than drugs or surgery (Grant 2000). Galen later related food to both disease and the restoring of health through its effect on the balance of "humours". In his writing, he refers to various types of foods including wafer biscuits, wheat flour, sour milk

and cheese causing the formation of kidney stones. Other foods, for example chickpeas and watermelon seeds, were considered to breakdown stones formed in the kidney. Juniper berries, dried and fresh figs cleansed the kidneys. He discouraged the consumption of kidneys from animals which he deemed unwholesome, full of "bad juices", smelling of urine and difficult to digest (Grant 2000). However, there are no early references to diet in relation to CKD.

Low protein diets for pre-dialysis patients

A historical account of diet therapy for renal patients has been provided by Giovannetti (1989). In the 1800s, a milk diet and bed rest were prescribed but are now recognised as undesirable due to the high protein and phosphate content of milk. The beneficial effects of a low protein diet were documented in 1918 by Franz Volhard who observed that this was associated with a delay in the rise in serum urea levels in patients with CKD. In addition, these patients did not suffer symptoms such as itching and nausea which are associated with uraemia (Giovannetti 1989).

In the 1960s, renal patients were advised to follow a low protein diet based on the work of Giordano (Giovannetti 1989). He demonstrated that a very low protein diet supplemented with essential amino acids achieved nitrogen balance and limited the production of nitrogenous waste products in the body. In addition to being low in protein, these diets were also low in phosphate. However, to achieve the therapeutic effect patients had to consume adequate energy from carbohydrates and fats. By the end of the 1960s, various low protein diet studies had been conducted and the recommended intake for predialysis patients was set at 0.6g of protein and 9.7mg of phosphate per kilogram ideal body weight per day (Giovannetti 1989). This is equivalent to a daily phosphate intake of 700mg for a 70kg man. To achieve this level of protein restriction, it was necessary to incorporate cereal products into the patients' diet which had to be low in both protein and phosphate. To help patients adhere to their modified diets a range of commercial low protein products, for example low protein flour, bread, pasta and biscuits, was produced commercially and made available on prescription for patients with kidney disease (Vennegoor 1982). Since the aim of low protein diets was to slow down the rate of progression of CKD, these patients required intensive counselling and close monitoring by specialist renal dietitians, which was labour intensive. Dolecek et al (1995) reported that patients prescribed a low protein diet required significantly more dietetic time than those who were following a normal protein diet. By the end of the 1990s more liberal daily protein intakes of 0.8g of

protein per kilogram ideal body weight per day, were being prescribed for the predialysis population. This change in practice could have been linked to the emerging evidence that the nutritional status of patients as they commenced haemodialysis was a good predictor of their nutritional status after 1-2 years on haemodialysis (Kopple 1997). Also clinicians acknowledged that some patients found it difficult to adhere to more restrictive low protein diets (National Kidney Foundation 2000).

Higher protein diets for haemodialysis patients

Concurrent to the work on low protein diets in the 1960s, haemodialysis was introduced as a treatment for patients with advanced CKD. As haemodialysis became a routine treatment the trend for nephrologists to prescribe low protein diets in order to slow the progression of CKD declined. Since the late 1970s, in contrast to pre-dialysis patients, those undergoing regular haemodialysis were advised to consume a diet containing 1.2g of protein per kilogram per ideal body weight per day (Gentile et al., 1989). The higher protein requirement was based on the fact that patients had greater nitrogen losses when they were undergoing haemodialysis and, therefore, needed to consume more protein on non-dialysis days to compensate for this. Loss of amino acids, via dialysis fluids was a contributory factor to a negative nitrogen balance (Gentile et al., 1989, Kopple 1997). Haemodialysis patients require the same daily energy intake as predialysis patients (35 calories per kilogram per ideal body weight) to prevent malnutrition and to achieve the protein-sparing effect associated with achieving optimal energy consumption (Gentile et al., 1989, National Kidney Foundation 2000).

Dietary phosphate restriction for haemodialysis patients

It has already been mentioned that a diet low in protein will also have a reduced phosphate content (Gentile et al., 1989, Snetselaar et al., 1994). For haemodialysis patients a dietary phosphate restriction of 800 - 1000mg/day was recommended (Gentile et al., 1989). This is based on the fact that those undergoing regular haemodialysis should consume more protein to meet their increased nutritional requirements, as previously discussed (Gentile et al., 1989). Rufino et al (1998) demonstrated that haemodialysis patients who consume a diet containing 1.2g of protein per kilogram ideal body weight per day were also consuming approximately 1400mg of phosphate. Since the standard haemodialysis treatment of only 4-hour sessions three times per week removes significantly less phosphate than healthy kidneys filtering blood continuously, haemodialysis patients are at risk of hyperphosphataemia and its associated medical complications. The challenge for

renal dietitians has been to counsel haemodialysis patients on how to achieve an intake closer to the recommended 1000mg of dietary phosphate per day and maintain an adequate protein intake. This is to ensure that these patients achieve and maintain a well nourished state. Daily protein and phosphate requirements are summarised in Table 1.2. In conjunction with dietary phosphate restriction, the development and implementation of phosphate binder drug therapy, as part of routine phosphate management has been a necessity.

Table 1.2 Dietary protein, energy and phosphate requirements for chronic kidney disease and dialysis patients (National Kidney Foundation 2000, 2004)

Nutritional Variable	Chronic Kidney Disease (Stages 3 - 5)	Haemodialysis
Protein (g / kilogram ideal body weight)	0.6 – 0.8	1.2
Energy (kcal / kilogram ideal body weight)	30 - 35	30 - 35
Phosphate (mg)	<800	800 - 1000

Phosphate binders

The term phosphate binder refers to oral drugs whose action is to bind to phosphate in foods whilst they are in the GI tract, thereby reducing the amount of dietary phosphate that is absorbed into the blood. The use of different types of phosphate binders has changed over the last 40 years. Malluche et al (2002) describe how in the 1970s researchers focused on the role of hypocalcaemia and hyperphosphataemia in the development of secondary hyperparathyroidism and renal bone disease. During this time, aluminium-based salts were widely used due to their efficient phosphate binding properties. However there were concerns regarding their long term use as early as the mid-1970s when it was discovered that some aluminium was absorbed and that prolonged use of aluminium-based phosphate binders led to the accumulation in the body, causing severe bone and brain disease (Alfrey et al., 1976). As a consequence, calcium-based phosphate binders were introduced but unfortunately, due to the quantity of calcium-based phosphate binders prescribed to

patients an increased incidence of hypercalcaemia and progressive metastatic calcification was observed (Altmann 2001). The significance of these health risks and mortality rates will be discussed in section 1.6.4.

Studies were also conducted in the 1980s using magnesium hydroxide as a phosphate binder but it was found to be associated with diarrhoea and hypermagnesaemia even at suboptimal therapeutic doses. Therefore, magnesium-based phosphate binders are not used as an alternative to calcium-based binders (Altmann 2002).

The last decade has seen the development of new phosphate binders which are both calcium-free and aluminium-free. Studies using sevelemer hydrochloride have demonstrated this compound can lower serum phosphate levels without causing a simultaneous rise in serum calcium levels (Bleyer et al., 1999, Altmann 2002).

Lanthanum is a rare earth metal which is found in trace amounts in the body. Lanthanum chloride hydrate was initially tried as a phosphate binder, but in a longer term study, of 100 days, it was found to accumulate in the liver, lungs and other tissues in rats (Graff et al., 1995). Lanthanum carbonate, has been tested as a phosphate binder, as it is much less soluble than lanthanum chloride. The results indicated that lanthanum carbonate could be an effective phosphate binder however the long term safety, in humans, needed to be investigated (Malluche et al., 2002). Table 1.3 summarises the key developments regarding phosphate binders as a treatment.

Haemodialysis

The last of the three treatments, used to control serum phosphate levels is haemodialysis. The Romans appeared to have some understanding about the need to remove toxins from the body and attempted to do this by giving hot baths to patients to remove urea. The action of the hot water made the patient sweat profusely and this, together with the toxins diffusing through the skin into the bath water, would temporarily relieve symptoms but leave the patient feeling tired. This technique continued to be used occasionally in more modern times even as late as the 1950s (Smith et al., 2003).

A detailed historical account of the significant developments which led to haemodialysis becoming a life saving treatment has been published (Smith et al., 2003). Haemodialysis was developed at the beginning of the 20th century based on the physical properties of membranes discovered by the Scottish chemist, Thomas Graham, in 1854. The significant developments in haemodialysis are summarised in Table 1.3. The basic kinetics of haemodialysis have already been explained in section 1.3 and will be discussed further in section 1.6.5. By the beginning of the 1970s, more renal patients were able to receive

haemodialysis due to the increased availability of haemodialysis machines in hospital and community settings.

In summary

Since the 1960s, restricting dietary phosphate intake, prescribing phosphate binders and providing haemodialysis have been the components of phosphate management. However, the limitations of these treatments have led to a reassessment of clinical practice used to manage mineral metabolism disorders. The following section will provide a current perspective of these treatments.

Table 1.3: Key developments regarding phosphate binders and haemodialysis as treatments for patients with chronic kidney disease.

Date	Observation / Discovery	Reference
1854	Graham used the term "dialysis" to describe the transport of solutes through an ox bladder	Smith et al 2003
1889	Richardson dialysed living animals, in experimental conditions, using man-made colloidion membranes	"
1914	First publication on the technique of haemodialysis entitled "the artificial kidney" (Abel 1914)	"
1920s	Haas performed six haemodialysis treatments on six patients	Clark 2000 Smith et al 2003
Late 1950s	Kolff's rotating drum dialyser used to treat patients with acute renal failure secondary to war injuries, drug overdose and poisoning	Smith et al 2003
1960s	Haemodialysis used as routine treatment for renal failure	"
1964	The first patient to be placed on overnight home haemodialysis	"
1970s	Emergence of satellite haemodialysis units The introduction of hemodiafiltration Aluminium-based phosphate binders were first used	" Malluche et al 2002
1980s	Calcium-based phosphate binders replaced aluminium-based phosphate binders as first line treatment Studies were also conducted using magnesium hydroxide as another potential phosphate binder	"
1995	Lanthanum identified as a potential aluminium-free phosphate binder. Studies performed on rats using lanthanum chloride hydrate	"
1998	Sevelamer hydrochloride was approved by the U.S. Food and Drug Administration for use as calcium-free, aluminium-free phosphate binder	"
1999	Studies performed on rats and dogs using lanthanum carbonate	"
2001	Toxicology studies report a dose dependent accumulation of lanthanum carbonate in the bones of rats. Similar mineralisation defects and osteomalacia were found in rats treated with sevelamer hydrochloride	"

1.6 Current Perspective of Phosphate Management

1.6.1 Biochemical targets

National and international serum biochemistry targets have been developed as a result of the body of evidence linking altered serum biochemical levels to increased rates of morbidity and mortality (The Renal Association 2002, National Kidney Foundation 2004, The Renal Association 2007 (Table 1.4).

The guidelines of The Renal Association (2002) are included because this document provided the most up-to-date biochemical targets at the time when the present research proposal, phosphate management protocol and algorithms were produced. The Renal Association clinical practice guidelines for haemodialysis (2007) have been included to demonstrate how the UK guidelines have been revised in line with the target values used by National Kidney Foundation (2004).

Table 1.4: National and international serum biochemical targets

	Target Values		
Serum Variables	The Renal Association 3rd Edition 2002	National Kidney Foundation 2004	The Renal Association 4th Edition 2007
Phosphate	<1.8 mmol/1	1.13 – 1.78 mmol/1	1.1 – 1.8 mmol/1
Corrected calcium	2.2 – 2.6 mmol/1	2.10 – 2.37 mmol/1	No values stated "pre-dialysis serum calcium, adjusted for serum albumin, should be within the normal range"
Calcium – phosphate product	No standard	<4.4 $mmol^2/l^2$	< 4.8 $mmol^2/l^2$
Intact parathyroid hormone	<4x upper limit of normal assay for patient who have been on haemodialysis for longer than 3 months *(normal range: 3 – 8 pmol/1)*	16.5 – 33.0 pmol/1	2 – 4x upper limit of normal assay *(normal range: 3 – 8 pmol/1)*
Aluminium	No patient whose ferritin level is <100ug/1 should have a serum A1 level > 2.2µmol/1	<0.7µmol/1 (or <20µg/1)	No values stated

1.6.2 Prevalence of hyperphosphataemia

In the first section of this chapter the aetiology of hyperphosphataemia in the haemodialysis population has been explained. It is also important to consider the prevalence of hyperphosphataemia in this patient group.

Table 1.5 summarises prevalence data published within the last six years (Johnson et al., 2002, Stevens et al., 2004, Hecking et al., 2004, The Renal Association 2007). It can be seen that there are problems in comparing the results of different studies, due to the inconsistency in the definition of hyperphosphatamia ranging from 1.8 – 2.42mmol/l. A comparison of results published by Stevens et al (2004) for Canada with The Renal Association (2007) for the UK was feasible as the data were based on the same definition of hyperphosphataemia (serum phosphate level >1.8mmol/l). The average prevalence rates in the Canadian and UK haemodialysis populations were 38% and 35% respectively.

A prospective, observational study by Hecking et al (2004) examined random samples from haemodialysis patients in five European countries including France, Germany, Italy, Spain and the UK. The overall average prevalence of hyperphosphataemia (serum phosphate level >2.10mmol/l) was 24%. The values ranged from 16% in Italy to 39% in Germany compared to 22% in the UK. For serum phosphate levels greater than 2.42mmol/l, the overall prevalence across Europe was 12% with levels in individual countries ranging from 4% in Italy to 22% in Germany compared to 12% in the UK.

These prevalence rates provide the evidence that hyperphosphataemia remains a challenge in renal units in the developed world. Consequently, haemodialysis patients will need to be closely monitored for the complications associated with hyperphosphataemia. These will now be discussed.

Table 1.5: Prevalence of hyperphosphataemia in haemodialysis patients

Study authors (year)	Association report (year)	Patient population (HD/PD)	Serum level (mmol/l)	Prevalence (%)
	The Renal Association UK Renal Registry (2007)	HD	>1.8	35
Stevens et al (2004)	----------	HD	1.78 – 1.94	8
			1.95 – 2.26	17
			> 2.26	13
Hecking et al (2004)	----------	HD	> 2.10	24
			> 2.42	12
Johnson et al (2002)	----------	HD / PD	>1.94	32

1.6.3 Complications associated with hyperphosphataemia

Secondary and tertiary hyperparathyroidism

Secondary hyperparathyroidism (SHPT) occurs when the parathyroid gland is stimulated to produce iPTH in response to either hyperphosphataemia or hypocalcaemia (Altmann 2001). This has been explained in section 1.3. Serum target iPTH levels have been included in the national and international serum biochemistry targets (National Kidney Foundation 2004, The Renal Association 2007) (Table 1.4). The average prevalence of serum iPTH level > 32pmol/l for UK haemodialysis patients, published by The Renal Association (2007), was 39%.

Block et al (1998) highlighted that a major clinical significance of SHPT is that it can lead to accelerated resorption of bone, a condition known as renal bone disease or renal

osteodystrophy. Patients can experience painful bones which can become weak leading to bone fractures (National Kidney Foundation 2004). A persistently raised serum phosphate level or low serum calcium level results in overstimulation of the parathyroid glands. At this stage the parathyroid glands become enlarged and continue to produce iPTH despite the fact that the serum calcium level may have returned to normal or exceeded the normal range. This is known as tertiary hyperparathyroidism which is defined by an elevated serum iPTH greater than 55pmol/l and possibly hypercalcaemia (serum corrected calcium level >2.74mmol/l) (National Kidney Foundation 2004). Traditionally, the treatment for tertiary hyperparathyroidism has been a partial or total parathyroidectomy. However, a new drug

treatment, cinacalcet hydrochloride, has been developed with the specific action of suppressing the parathyroid gland and subsequently lowering serum iPTH levels (Torres 2006). This drug has now been implemented into routine clinical practice for treating SHPT and thereby reducing the need for patients to undergo surgery.

Calcium x phosphate product

Another serum variable, included in the clinical guidelines is calcium x phosphate product (National Kidney Foundation 2004). An elevated serum CaxP product, defined as >4.44mmol^2/l^2, can occur due to hyperphosphataemia, hypercalcaemia or a combination of both. The average prevalence of serum CaxP product >4.44mmol^2/l^2 for haemodialysis patients, published by The Renal Association (2007), was 30%. In comparison, Johnson et al (2002) reported that, during a three month survey period, 3% of both haemodialysis and peritoneal dialysis patients had an average serum corrected calcium level > 2.78mmol/l. Whereas 32% of patients had a serum phosphate level > 1.94mmol/l. These results suggest that the incidence of elevated serum CaxP product is likely to be due to hyperphosphataemia rather than hypercalcaemia. The clinical significance of elevated serum CaxP product is that it has been associated with an increased risk of soft tissue calcification (National Kidney Foundation 2004), which will now be discussed.

Soft tissue calcification

Hyperphosphataemia, elevated serum iPTH level, bone resorption and the use of calcium-based phosphate binders can result in precipitation of calcium and phosphate salts. These salts travel in the blood and deposit in soft tissues around the body, including the heart and its valves, blood vessels, lungs, kidneys, joints, eyes and skin (Rogers et al., 2007).

Calciphylaxis, also known as calcific uraemic arteriolopathy, is defined as calcification of small blood vessels with associated tissue necrosis. It mainly develops on lower limbs but can also affect the abdominal wall and male genitals (Rogers 2007). Significantly soft tissue calcification, especially cardiovascular, has been observed in younger haemodialysis patients. It has also been associated with increased mortality rates in the haemodialysis population (Goodman et al., 2000). Valvular calcification has also been found to occur in dialysis patients who had a CaxP product $<4.44 mmol^2/l^2$ (Ribeiro et al., 1998). This finding emphasises the necessity for strict serum phosphate and calcium control as stated in the clinical guidelines (National Kidney Foundation 2004, The Renal Association 2007).

Apart from the unpleasant pathologies caused by complications associated with hyperphosphataemia, the recent published evidence of increased mortality rates in the haemodialysis population is a serious cause for concern. This will now be discussed.

1.6.4 Mortality rates

Hyperphosphataemia and mortality

Two recent studies have emphasised the mortality risk for hyperphosphataemia. The data published by Block et al (2004) were adjusted for both demographic data and serum variables and used a serum phosphate reference range of 1.29 – 1.61mmol/l. Block et al (2004) showed that as the serum phosphate level rose above the reference range the risk of death increased (Table 1.6). Stevens et al (2004) published mortality rates for the Canadian dialysis population. The results shown in Table 1.6 demonstrate that once the serum phosphate level reached 1.95mmol/l or above, a further rise in serum phosphate level resulted in a significantly increased risk of death, when compared to a reference serum phosphate level of less than 1.78mmol/l.

Table 1.6: Mortality rates associated with hyperphosphataemia

Study authors (year)	Patient population (HD/PD)	Serum level (mmol/l)	Mortality Rates		
			Mortality risk[a] or risk ratio[b]	95% Confidence Intervals (CI)	P value
Block et al (2004)	HD	1.29 – 1.61	1.00[a]	*	*
		1.61 – 1.94	1.07[a]	*	*
		1.94 – 2.26	1.25[a]	*	*
		2.26 – 2.58	1.43[a]	*	*
		2.58 – 2.91	1.67[a]	*	*
		>2.91	2.02[a]	*	*
		> 3.55	2.47[a]	1.90 – 3.19	*
Stevens et al (2004)	HD / PD	<1.78	1.00[b]		
		1.78 – 1.94	1.32[b]	0.79 – 2.22	0.293
		1.95 – 2.26	1.53[b]	1.02 – 2.30	0.039
		2.26	1.82[b]	1.16 – 2.84	0.009

*No values published

Calcium x phosphate product and mortality

Block et al (2004) also published data for the mortality risk associated with CaxP product. These data were also adjusted for both demographic data and serum variables and used a serum CaxP product reference range of 3.23 – 3.65 $mmol^2/l^2$. The results in Table 1.7 indicate that even within the current target range of <4.44 $mmol^2/l^2$ the mortality rate was 1.14 (95% confidence intervals (CI):1.05 – 1.23). Stevens et al (2004), also published mortality rates for serum CaxP product. Table 1.7 shows that once the serum CaxP product exceeded 5.64$mmol^2/l^2$, this resulted in a statistically significant mortality risk ratio of 1.85; 95% confidence intervals (CI), 1.10 – 3.11; P = 0.02.

Statistical analyses have provided evidence to highlight that hyperphosphataemia is significantly associated with mortality in the haemodialysis population. In order to

minimize the effect of hyperphosphataemia a combination of dietary phosphate restriction, phosphate binder medications and haemodialysis continue to be the treatments available.

Table 1.7: Mortality rates associated with serum calcium-phosphate product

Study authors (year)	Patient population (HD/PD)	Serum level ($mmol^2/l^2$)	Mortality Rates		
			Mortality risk[a] or risk ratio[b]	95% Confidence Intervals (CI)	P value
Block et al (2004)	HD	3.23 – 3.65	1.00[a]	*	*
		3.65 – 4.02	1.06[a]	0.98 – 1.15	*
		4.00 – 4.44	1.14[a]	1.05 – 1.23	*
Stevens et al (2004)	HD or PD	< 4.43	1.00[b]	*	*
		4.43 – 4.84	0.76[b]	0.42 – 1.39	0.382
		4.84 – 5.64	1.45[b]	0.92 – 2.29	0.108
		>5.64	1.85[b]	1.10 – 3.11	0.020

*No values published

1.6.5 Current treatments for hyperphosphataemia

Neutral phosphate balance

Kuhlmann (2007) defines the ultimate goal in phosphate management as achieving a neutral phosphate balance. Haemodialysis patients are advised to follow a diet containing 1000mg of phosphate per day (Locatelli et al., 2002, Cupisti et al., 2003). However, the daily amount of phosphate absorbed in the GI tract has been reported as 50 - 70%, which is equivalent to a maximum of 700mg of phosphate per day (National Kidney Foundation 2004, Kuhlmann 2007). The main route of phosphate excretion for haemodialysis patients is via the haemodialysis machine and the average amount of phosphate removed during a standard 4-hour conventional haemodialysis session is 800mg (Cupisti et al., 2003, Pohlmeier et al., 2001, Kuhlmann 2007) for a person undergoing haemodialysis three times per week, this is equivalent to a mean loss of only 340mg/day (Kuhlmann 2007). Therefore the amount of phosphate removed from the blood is insufficient to achieve a neutral phosphate balance even on a restricted phosphate intake. This explains why, without the

use of phosphate binders, haemodialysis patients are at risk of long-term hyperphosphataemia. However, haemodialysis patients are still routinely counseled and encouraged to follow a low phosphate diet as in theory good dietary adherence should equate to lower doses of phosphate binders being required.

Renal nutrition

This section will discuss strategies on how dietary management can help haemodialysis patients achieve a neutral phosphate balance.

The current daily protein requirement for haemodialysis patients is 1.2g/kg/day (Locatelli et al., 2002, Kuhlmann 2007) but the dietary analysis undertaken by Rufino et al (1998) found a strong positive correlation between protein and phosphate intake ($r = 0.89$, $P< 0.001$) in their haemodialysis population. Therefore, current dietary phosphate management faces a dilemma because foods rich in protein are also rich in phosphate. Concerns regarding whether it is possible to counsel haemodialysis patients on how to achieve a phosphate restricted diet without compromising protein intake were addressed by Cupisti et al (2004). This study achieved, a mean reduction of 100mg dietary phosphate, $P<0.05$, without significantly lowering protein intake. This study enabled patients to achieve a reduction in their dietary phosphate intake by including advice on which protein rich foods contained the least amount of phosphate. The recommended acceptable phosphorus-protein is 10-12mg phosphate per g of protein (Cupisti et al., 2003). Tables listing a variety of foods and beverages which can be used to counsel patients on dietary phosphate restriction have been compiled and published (National Kidney Foundation 2004, Cupisti et al., 2004).

Haemodialysis patients are encouraged to eat a varied diet as much as possible. Even the most motivated patients may find it difficult to comply with choosing the most suitable foods in the long-term. Therefore, in reality, a combination of dietary phosphate restriction and oral phosphate binders is necessary to achieve target serum phosphate levels.

Phosphate binders

The types of binder used in current practice are clearly stated in K/DOQI guidelines (National Kidney Foundation 2004). Specific instructions are provided on limiting the total dose of calcium-based binders to prevent patients ingesting more than 1500mg elemental calcium per day. Calcium-based binders can continue to be used as first line therapy in the absence of hypercalcaemia (Quinibi et al., 2004). When non-aluminium binders, used as monotherapy, are ineffective and the serum phosphate level is greater than 2.26mmol/l, the

recommendation states that aluminium-based binders can be used for a four week course of treatment only. Prolonged use of these binders has been contraindicated due to the associated health risks, for example aluminium bone disease or neurotoxicity (National Kidney Foundation 2004). This guideline is also based on the evidence from a study conducted by Sheikh et al (1989) which demonstrated that aluminium possessed a more effective phosphate binding capacity than calcium and magnesium based binders.

Sevelemer hydrochloride, has been described as the ideal phosphate binder due to the fact that it is safe, well tolerated, palatable, non–absorbable and has good efficacy and specificity (Malluche et al., 2002). Consequently, it has also been recommended for use as first line therapy, especially in cases when the serum corrected calcium level is elevated (National Kidney Foundation 2004). In 2007, lanthanum carbonate was approved for use, in the UK, and is an alternative non-calcium, non-aluminium phosphate binder to sevelemer hydrochloride (Finn 2006).

Haemodialysis adequacy

Once haemodialysis became a routine treatment in the 1970s, patients who commenced haemodialysis underwent regular serum biochemistry tests and a subjective assessment of their health to determine the effectiveness of haemodialysis. By the 1980s researchers began work to develop an objective method to measure dialysis adequacy (Thomas 2003). Urea kinetic modelling is a complex concept which has been summarised in a mathematical equation which calculates urea removal, from the blood, and is routinely used as a measure of dialysis adequacy (Daugirdas 1993, 2001).

Daugirdas (1993) explains in detail how dialysis adequacy is described by the term Kt/V whereas Kugler et al (2005) provides a basic definition of Kt/V as follows:-

K = efficiency of the dialyser to remove urea (L/hr)

t = treatment time per dialysis session (hr)

V = total volume of urea in the body (L)

The significance of dialysis adequacy has been explained by Daugirdas (2001). A value of Kt/V of less than 0.8 has been associated with increased risk of morbidity and poor treatment outcome. The National Kidney Foundation (1997) recommended a minimum Kt/V>1.2, for patients receiving haemodialysis three times weekly, based on improved survival data obtained from retrospective studies. A more detailed equation for Kt/V can be found in chapter 3.

In summary

Neutral phosphate balance can only be achieved by restricted dietary phosphate intake in combination with the use of oral phosphate binders and optimising the haemodialysis prescription to limit the amount of phosphate in the blood.

1.6.6 Evaluation of phosphate education and knowledge in haemodialysis patients

Traditionally, patients are taught about the importance of both their diet and medication at the start of regular haemodialysis and this is reinforced as treatment continues. Due to the prevalence of hyperphosphataemia, discussed previously, it is necessary to evaluate the effectiveness of this education.

Phosphate education

A number of studies have evaluated the efficacy of phosphate education in the dialysis patient population. Although some were able to show a clinical benefit, other studies did not.

Prowant et al (1989) believed that patients required adequate information regarding phosphate management to motivate them to adhere to their treatments. They conducted a study using a phosphate education program which they had developed. The program was piloted on 35 dialysis patients, of which 21 patients were on haemodialysis. All of the recruited study patients had elevated serum phosphate levels (>1.94mmol/l) for at least three months in the previous year. The patients also underwent the same phosphate knowledge test both pre- intervention and six weeks post intervention. The researchers found no significant difference between the pre- and post-intervention mean serum phosphate levels or phosphate knowledge scores for the HD patients. In comparison, statistically significant improvements in results were achieved with the peritoneal dialysis patients. The mean serum phosphate level decreased from 1.99±0.34mmol/l to 1.86±0.19mmol/l, ($P < 0.025$). These patients also significantly increased their phosphate knowledge score, post intervention from 57.7% to 69.6%, ($P < 0.01$). This small study suggests that this education program can be effective although the peritoneal dialysis patients were taught by their primary nurse at a routine clinic visit whereas the haemodialysis patients were taught by a renal dietitian whilst they were on dialysis. Therefore the groups are not directly comparable and the study should be repeated, as a randomised controlled study, ensuring that the same member of staff educates all of the study patients. Also the same location should be used for educating the patients if possible.

Nine years later Schlatter et al (1998) published their study which tested the effectiveness of an individual education session, provided by a renal nurse, to 29 haemodialysis patients. These patients also underwent a phosphate knowledge test both pre-intervention and three weeks post-intervention. On this occasion the researchers found no significant difference between the pre- and post-intervention mean serum phosphate levels. However, post intervention mean phosphate knowledge scores increased significantly ($P < 0.01$). Neither of these studies were able to achieve a reduction in serum phosphate levels, in HD patients, 3 - 6 weeks post education by renal nurses (Prowant et al., 1989, Schlatter et al 1998).

Ashurst et al (2003) conducted a randomised control trial with 56 hyperphosphataemic patients, defined as serum phosphate > 1.7mmol/l, and found that a phosphate education package was an effective tool for lowering serum phosphate levels, when used by an experienced renal dietitian, for teaching individual haemodialysis patients. For the intervention and control groups, the mean change in serum phosphate level was -0.36mmol/l; (95% CI, -0.54 to -0.16, P=0.02) and -0.07mmol/l; (95% CI, -0.11 to +0.2, P=0.37 respectively. Post intervention, only the intervention group achieved a target mean serum phosphate level of 1.6mmol/l. It must be noted that the follow-up period for this study was three months which in this case was sufficient time to observe a significant improvement in serum phosphate levels in the intervention group only. However, iPTH levels were not reported which would have provided relevant secondary outcome data in this patient group. Despite the patients receiving phosphate education, their knowledge was not tested.

Studies conducted to determine whether patients' phosphate knowledge is associated with serum phosphate control have shown that some education programmes can have some beneficial effects but a positive relationship between these two variables have not been proven.

Phosphate knowledge

Phosphate knowledge has also been tested in the haemodialysis population, in the absence of an education intervention.

Stamatakis et al (1997) conducted an observational study on 21 dialysis patients, of which 17 patients were on haemodialysis. The patients were stratified into one of two groups dependent on their serum phosphate level. The moderate and severe hyperphosphataemic groups had serum phosphate levels between 1.45 – 2.26mmol/l and greater than 2.26mmol/l respectively. The patients in the moderate group were found to have significantly higher phosphate knowledge scores than the patients in the severe group (P =

0.028). Since the study group contained patients on both types of dialysis treatment it would be beneficial to repeat the study using only haemodialysis patients, to determine whether the same results could be achieved in that population. It should be stated that the content of the education is the same for both PD and HD patients but the location for the education differs. PD patients are generally seen in an out-patient clinic setting whereas HD patients are routinely advised whilst on HD. It is possible that PD patients will be more receptive to the information given in contrast to HD patients who may have a tendency to feel nauseous and become hypotensive during dialysis. The most appropriate time to educate HD patients will be discussed in more detail in chapter 5.

Poduval et al (2003) carried out a survey to evaluate haemodialysis patients' level of education and their phosphate knowledge. The researchers found that 74% of patients were unable to identify foods rich in phosphate and 61% of the patients did not know the complications associated with an elevated serum calcium-phosphate product. The level of college education was also documented for this survey and the researchers found that the patients with the lowest levels of education were more likely to have an elevated CaxP product (P=0.04). Other relevant studies published between 2003 – 2008 will be discussed later in chapter 5.

Education strategies

It is clear from the results obtained, in the studies previously described, that effective education is achievable, in some cases. In the 21st century, renal health professionals should be encouraged to develop and evaluate new education strategies in phosphate management. Renal dietitians should be able to draw upon education programmes developed, piloted and evaluated by other health professions also working in the field of nutrition. Tanumihardjo et al (2009) describe education strategies for weight reduction which have already been applied to renal patients, for example advising patients on how to replace high phosphate foods with low phosphate alternatives. Much emphasis has been placed on reinforcing the diet advice in conjunction with effective resources with the aim to ensure patients achieve both short and long term goals with regards to their health. Petrovici et al (2006) and Nagel et al (2008) have both highlighted that the education level of patients has often been identified as significant when assessing knowledge and incidence of co-morbidities. Therefore, documenting the education level patients' have attained and developing nutrition education resources to meet the needs of all the patients has been strongly recommended in the literature (Nagel et al., 2008). It has been suggested

that health professionals, involved in patient education, will also need to allocate more time to spend with patients of a lower intellect (Bland et al., 2008).

Foley et al (1998) targeted patients with low socioeconomic status to pilot healthy diet cooking sessions on a budget. The aim was to demonstrate that healthy eating was achievable on a limited budget. The researchers reported positive outcomes based on patients' self-reporting changes in dietary, shopping and cooking behaviour. A more robust evaluation of this programme should have been undertaken to determine its true effectiveness. Cooking sessions have also been incorporated into nutrition programmes for children, and have been reported as successful due to improved nutrition knowledge and skills to facilitate behavioural change (Anderson et al., 2001). Attempting low phosphate diet cooking sessions with HD patients would be an original project idea requiring the participation of very motivated patients.

Watters et al (2009) have categorised psychosocial factors associated with a dietary fat intake into the following: i) predisposing factors, for example individual's belief regarding the importance of a low fat diet and personal well-being, ii) reinforcing factor, which involved the importance of social support from family / carers and iii) enabling factor, which related the practicalities of adhering to a low fat diet. The authors also provided examples for predisposing factor stating that African Americans had a tendency to consume more fat than their white counterparts. Gender differences were also reported whereby men required more advice on the practicalities of adhering to a healthy diet. These results suggest that nutrition educators should be (i) aware of potential differences between different racial groups and genders and (ii) flexible in their approach when educating a diverse patient population.

These articles have provided some useful information and ideas which should be considered when educating renal patients. Education strategies, including learning styles and resources, will be discussed in chapter 5.

A document produced by the prescribing working party of The British Dietetic Association (2007) includes an example of phosphate management documentation produced by renal unit staff at Newcastle upon Tyne NHS Foundation Hospitals Trust. It is clearly stated that the aim is to enable renal dietitians to extend their role into managing patients' phosphate medication provided they successfully complete the necessary education and training and pass a competency assessment. A component of the competency assessment is the ability

to explain the aetiology of hyperphosphataemia and the long-term consequences. Therefore, as well as providing patients' with clear instructions on the necessary changes to their diet and medication regime, renal dietitians must also be able to educate the patients on all aspects of hyperphosphataemia. Phosphate protocols have been a recent major development in renal clinical practice and this shall now be discussed.

1.6.7 Protocols and algorithms

Historically, phosphate management has entailed the renal doctor having sole responsibility for managing patients' medications and the renal dietitian providing individual advice on a phosphate restricted diet. Since phosphate dietary restriction and initiation and dose adjustments of medication are fundamental to phosphate management it is logical that renal dietitians and renal pharmacists play a vital role in the development, implementation and evaluation of protocols used in clinical practice. The development of locally agreed protocols and algorithms is becoming more common as a way to incorporate national and international guidelines into clinical practice (Craven et al., 1996, Cannata-Andia et al., 2000, Johnson et al., 2002, Casey et al., 2006).

Johnson et al (2002) published results of a survey conducted in the Mid-Western states of North America in 1999, regarding mineral metabolism management in the dialysis units which provided care for both haemodialysis and peritoneal dialysis patients. This survey highlighted that despite 65% of the dialysis units stating a protocol was used, 32% of patients experienced an elevated serum phosphate level (>1.94mmol/l). To date the evidence to support the effectiveness of phosphate protocols is limited. Casey et al (2006) conducted a basic audit one year after a protocol was implemented and found that 15% more patients achieved the target serum phosphate level of <1.8mmol/l, compared to baseline, although the incidence of hyperphosphataemia remained relatively high at 24% this value was lower than the 35% prevalence rate quoted by the Renal Association (2007) (Table 1.5). Protocols will be discussed in more detail in chapter 2.

Johnson et al (2002) recognised that better coordinated patient education on a low phosphate diet, phosphate binders and vitamin D was an important part of phosphate management in the dialysis population. Therefore, a renal research team was formed at Barts and the London NHS trust consisting of renal consultants, pharmacists and dietitians. A research proposal was written which included a phosphate management protocol and a phosphate knowledge questionnaire and the purpose of this study was to pilot both on a haemodialysis population.

1.7 Aims of the study

Despite the current medical and dietetic treatments used in clinical practice to achieve and maintain acceptable serum phosphate levels, the current prevalence rates of hyperphosphataemia and the associated health risks, in haemodialysis patients, indicate that controlling serum phosphate levels remains a challenge in the 21st century. The aims of this study were two-fold, as follows:-

1) To evaluate the effectiveness of a new phosphate management protocol (PMP) designed to achieve serum phosphate levels set by The Renal Association (2002) and National Kidney Foundation (2004) for patients undergoing regular haemodialysis.

2) To evaluate patients' phosphate knowledge, pre- and post-intervention, regarding medical complications associated with hyperphosphataemia and treatments for managing serum phosphate levels in this patient population. Also to determine if there is a relationship between a change in serum phosphate level and change in knowledge post intervention.

To achieve the first of these aims a phosphate management protocol was piloted to enable the renal research pharmacists and a renal research dietitian to optimise patients' phosphate binders and the alfacalcidol (vitamin D analogue). This involved changing phosphate binder types and adjusting doses of both the binders and alfacalcidol. The hypothesis tested by this approach was that renal pharmacists and renal dietitians can help HD patients with hyperphosphataemia achieve target serum phosphate levels (1.13 – 1.8mmol/l), by following a defined PMP.

To address the second aim, a phosphate knowledge questionaire was designed, pilotted and subsequently used to investigate the knowledge of haemodialysis patients regarding the medical complications related to hyperphosphataemia and management of serum phosphate. The questionnaire included related complications, low phosphate diet, phosphate binders and haemodialysis. The hypothesis being tested was that a significant relationship exists between the change in patients' phosphate knowledge scores and the change in serum phosphate levels after a protocol is used to define phosphate management in haemodialysis patients for 4 months. The PMP group study patients' received phosphate education from the renal pharmacists and renal dietitians, as part of the protocol procedure. The methodology for this study will now be discussed in chapters 2 and 3.

Chapter 2: STUDY DESIGN

2.1 Original study design

2.1.1 Research project proposal

A randomised controlled two part study to evaluate the effectiveness of different education methods to achieve serum phosphate levels set by the Renal Association (2002) for haemodialysis (HD) patients

A) Purpose of proposed investigation

Hyperphosphataemia develops when renal function reaches 25% normal. Only 40% of the patients, with deteriorating renal function attending a pre-dialysis clinic had serum phosphate levels within the normal range. This illustrates that hyperphosphataemia is already a problem before patients commence dialysis.

The problem continues when patients are on HD due to the inability of HD to effectively remove the excess phosphate from the blood. In general, discussions with HD patients reveal a lack of knowledge regarding foods rich in phosphate, which tablets are their phosphate binders and when they should be taking them.

The renal multidisciplinary team believe that if our patients had a better understanding of the importance of their phosphate restricted diet and phosphate binder medication then their serum phosphate levels will also improve. The aim of this multidisciplinary team project is to determine the best method of educating HD patients to achieve serum phosphate levels set by The Renal Association (2002).

The duration of the project will be eighteen months (this includes writing up the study) and will take place at HD units at St. Bartholomew's, Royal London Hospitals, Whipps Cross and Wanstead Satellite Unit.

If we are able to determine an effective phosphate control education method then we will want to alter our working practices in the future as a result of this evidence based project.

B) Background of the project and literature search

This section has been omitted as it contained the same information as discussed in detail in chapter 1 of this thesis.

C) Plan of investigation

i) Phosphate knowledge questionnaire

This was originally designed with the help of the Clinical Effectiveness unit. It was then piloted on CAPD outpatients at St. Bartholomew's Hospital. Liz Paul (statistician) has advised us to change the style of the questionnaire from 'multiple choice' questions to interview with 'open' questions. This will also be piloted on CAPD patients prior to commencing the study.

ii*) Staff required for the study*

The following current BLT staff will carry out the study:-

- Senior I Renal Dietitian
- Senior Renal Pharmacist(s)

Funding has been obtained from BLT Research and Development department for the recruitment of staff to cover the researchers workloads during the study period.

iii) Organisation of the Trial

In 2000, ninety – seven haemodialysis patients had a serum phosphate level >1.7 mmol/l, the mean phosphate was 2.16 mmol/l with a standard deviation of 0.329. Liz Paul advised that a sample size of seventeen patients in each group will be required to detect a reduction of 15% in the mean phosphate level with a power of 80% at a significance level of 0.05. A minimum of 68 patients will be chosen from our HD patient population who fit the criteria stated below.

iv) Recruitment of subjects (3 months)

The inclusion criteria:-

- Stable adult patients on haemodialysis
- Consistent serum phosphate levels > 1.8 mmol/l
- Normal serum calcium levels : 2.2 – 2.6 mmol/l
- Acceptable intact parathyroid hormone (iPTH) levels : 0 – 100 pmol/l
- Dialysis Adequacy: Kt /V > 1.2 (HD thrice weekly)
  Kt /V > 1.8 (HD twice weekly)

v) Study design (see study flow chart)

This will be a random controlled trial of factorial design. The group factors:-

- Group advice sessions (Intervention I)
- Individual advice from renal research dietitian and renal pharmacist (Intervention II)
- Individual reviews, including advice, from another renal dietitian and a renal doctor (Standard practice)

The patients will be randomly assigned to one of four study groups (G1, G2, G3 and G4).

vi) Baseline Data Collection

We will obtain informed consent from the patients prior to administering a short phosphate knowledge questionnaire. This will be carried out by a member of the research team whilst the patients are undergoing HD.

The questionnaires will then be evaluated and the results will determine if hyperphosphataemia is due to poor understanding or non- compliance.

All HD patients have routine blood taken monthly which includes corrected calcium and phosphate levels. Intact PTH levels are checked every six months routinely. The only extra blood tests required are PTH levels which will occur twice during the study period.

vii) Study Phase I (2 months)

a) Group Advice Sessions (G1 + G2)

This time scale is required to enable us to carry out the group advice sessions to small patient groups at the various HD sites. It may be necessary to do separate teaching sessions in foreign languages. Patients will receive a one hour group teaching session run by the renal research pharmacist and renal research dietitian who will discuss phosphate binder medications, phosphate restricted diet and complications related to poor phosphate control. Patients will be given a summary of the session in the form of an information booklet. The doctors will review the patients' phosphate binder medication in clinic as usual.

Approximately two weeks after patients have attended a group session the same phosphate knowledge questionnaire and blood tests will be repeated.

b) Individual Advice Sessions (G3 + G4)

Patients will continue to receive our current standard practice, one - to - one teaching on the dialysis unit by a renal dietitian. The renal doctors will review the phosphate binder medication on the unit or at a dialysis clinic.

At the end of this study period, patients undergo the same phosphate knowledge questionnaire and blood tests will be repeated.

viii) Washout Period (1 month)

This has been included to determine whether any effects of the first study phase will still be present prior to patients commencing the second study phase.

ix) Study Phase II (4 months)

a) Individual Advice (G1+G3)

Each patient in this group will be seen on a one – to – one basis by a renal research pharmacist and the renal research dietitian. Each patient will have an individualised phosphate control care plan designed for them by the research team. Each patient will be seen once a month for four consecutive months.

At the end of this phase the phosphate knowledge questionnaire and blood tests will be repeated.

b) Individual Advice Sessions (G2 + G4)

See explanation given in Study phase I

One month after Study Phase II the phosphate knowledge questionnaire and blood tests will be repeated.

D) Statistical Analysis

The principal outcome measures are serum phosphate levels and phosphate knowledge scores. Formal statistical analysis will be undertaken. Analysis of variance and t-tests will be used to compare mean phosphate levels in the four study groups.

E) Dissemination of Results

A final report, conference presentations and publications in professional journals will be used to disseminate our findings.

F) Reason for Support Requested

A senior renal dietitian and senior renal pharmacist(s) are required as lower grades

require supervision. Additional resources will be required for the following:-

- Liz Paul our statistical adviser. Her recommendation of sample size justifies the duration of the study.
- Translators as it is feasible that some of the patients that we recruit, will not speak English as their first language. It is for this reason that we will need to have all of the written information translated into four languages. Also we will need an interpreter present at the separate group education sessions and the intensive counselling sessions.
- The clinical biochemistry department will be required to analyse additional iPTH levels for the study patients.

G) Arrangements for Supervision

The researchers will be supervised by Professor John Cunningham. He is also internationally renowned for his work in the field of Renal Bone Disease.

Dr Stan Fan will provide "in–house" medical support after Professor Cunningham leaves the trust at the end of June. We will arrange regular meetings with both renal consultants throughout the duration of the study.

H) Statement of how the research will benefit the trust

Allied Health Professionals are being encouraged to gain experience in research. We, the researchers, are keen to undertake an original research project as part of our professional development.

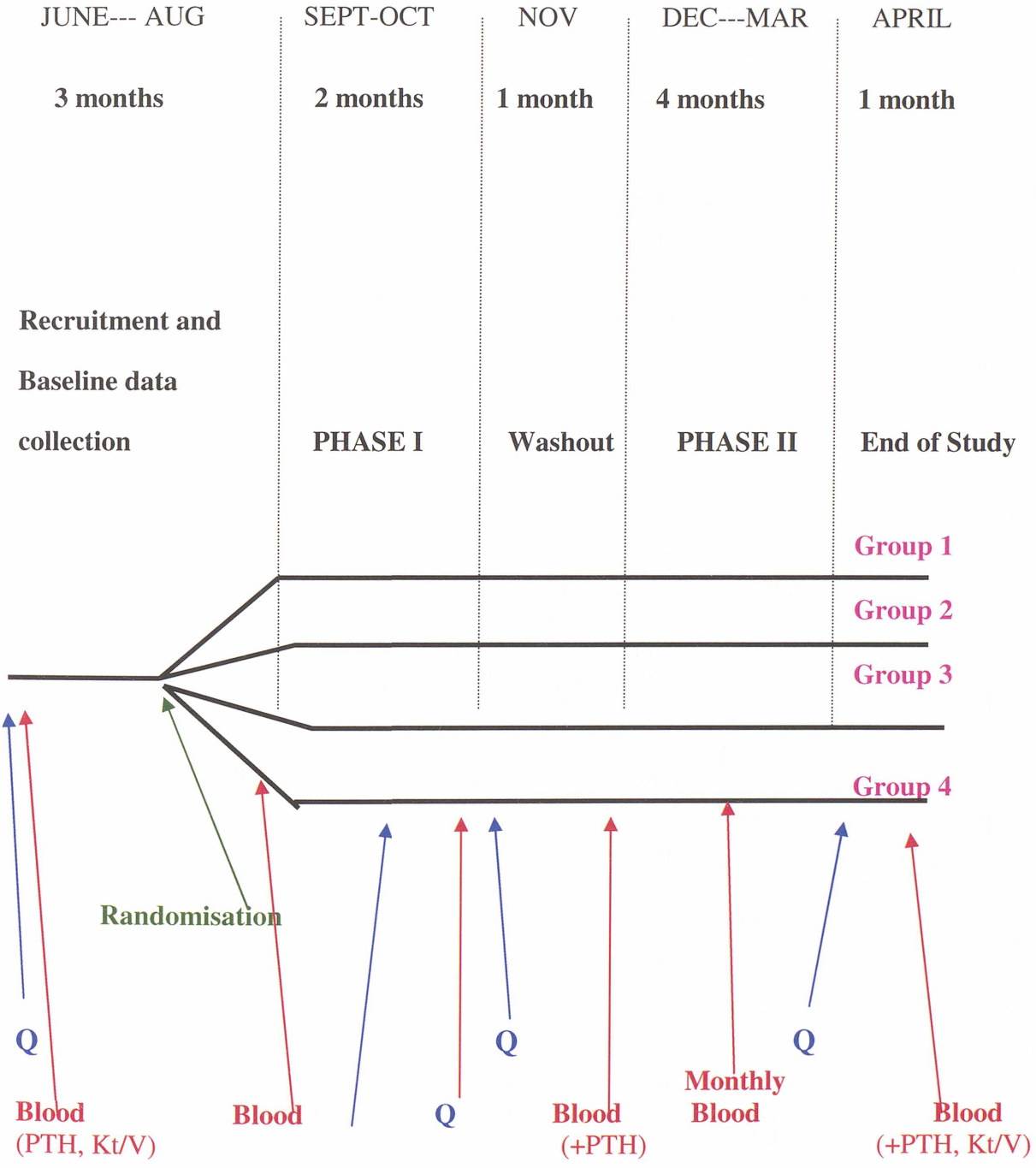
We also believe that multidisciplinary team research is the way forward to improving the clinical care we provide for our renal patients in this trust. As a result of this study we would aim to make recommendations with respect to changing our current practices in managing blood phosphate control.

Phosphate Research Project Team:

- names and contact details removed for security reasons

Author: Dawn Yokum May 2002

Figure 2.1: Study Flowchart



	Phase I	Phase II
Group 1 (G1)	Group advice	Individual advice (Protocol Group)
Group 2 (G2)	Group advice	Individual advice*
Group 3 (G3)	Individual advice (Standard Practice*)	Individual advice (Protocol Group)
Group 4 (G4)	Individual advice (Standard Practice*)	Individual advice*

2.1.2 Personal contribution to the research project

Summary notes of work undertaken

2001: i) Member of the original phosphate management research team

ii) Sought advice from a statistician regarding power calculation and phosphate knowledge questionnaire design

iii) Main author of the research project proposal and phosphate knowledge questionnaire (PKQ)

iv) Ethics application: Provided help and support to other team colleagues who completed and submitted the ethics committee application form, which was successful (see Ethics Committee Letters, Appendix 2.1)

2002: i) Lead for Barts and the London Trust (BLT) R&D department research project funding application, which was successful (See R&D Funding Approval Letter, Appendix 2.2)

ii) Participated in discussions with Shire Pharmaceutical Group PLC regarding a modest educational grant which was successful

iii) Phosphate management protocol (PMP):-

- Provided help and support to renal pharmacists in the development and submission to BLT Patient Group Direction (PGD) committee
- Attended the PGD committee meeting, with one of the renal pharmacists, where the protocol was approved for piloting as part of the research project

iv) Phosphate knowledge questionnaire (PKQ)

- Piloted and amended the PKQ

v) MPhil Degree

- Enrolled at London Metropolitan University as a part-time student (Dr Angela Madden (Director of Studies)

vi) Developed a presentation and resources on how to follow a low phosphate diet

2003: i) Recruited the study patients

ii) Informed Drs / Senior HD nurses about the study, recruited patients and group allocation

iii) Undertook data collection throughout the study

- Liaised with haemodialysis (HD) nurses, at each site regarding additional blood samples, for example intact parathyroid hormone samples, it was my

responsibility to ensure that these samples were in the clinical biochemistry laboratory and centrifuged within an one hour of collection for the analysis to be viable.

iv) Led regular research team update meetings

iv) Organised and conducted group education sessions with one of the renal pharmacists

v) Conducted renal dietetic reviews for patients in the PMP intervention group

2004: i) Completed data collection

ii) Statistical analysis

- Regular meetings with statistician

2005: i) Submitted abstract to European Dialysis Transplant Nurses Association (EDTNA) annual conference which was accepted for an oral presentation

ii) Oral presentation as part of phosphate management session at the EDTNA conference in Vienna

2005 – 2009: Dissemination (a) MPhil thesis and b) Writing for publication involved:-

i) Statistical analysis

- Regular meetings with statistician

ii) Regular contact and meetings with Dr Angela Madden

iii) Collaboration with the rest of the research team on the manuscript

iv) Nov 2008: Article published in Journal of Renal Nutrition (See copy as insert at the back of the thesis)

v) Jan 2009: MPhil thesis submission

2.2 Original study design

This study was originally designed to be a two-part, randomised controlled trial. Data collection started in June 2003 but recruitment was much slower than anticipated, predominantly because more eligible patients refused to participate than had been anticipated. It became apparent that the target number of 68 completed subjects would not be achieved within the funded time available. In addition, the education sessions which were being run for groups of patients were frequently attended by only one or two patients and, therefore, did not differ substantially from the standard, individualised education with

which they were being compared. As a result, it was decided to continue the study in a simplified format and it is this which has been written up for this thesis. The original study design has been described in detail in the previous section.

2.3 Final study design

The study undertaken was a single randomised controlled trial using two study groups, Phosphate management protocol (PMP) group and Standard practice (SP) group.

The study examined:-

a) The effectiveness of a PMP, used by a renal research dietitian and renal research pharmacists, to optimise serum phosphate levels in a haemodialysis patient population.

b) The phosphate knowledge of all study patients in both groups, both at baseline and at the end of the study, using a phosphate knowledge questionnaire which was designed specifically for the purpose of this study.

2.4 Development of the Barts and the London NHS Trust (BLT) Phosphate Management Protocol

2.4.1 Patient group direction

Background

Historically, the pharmaceutical management of individuals with long term clinical conditions, for example chronic kidney disease, has been the domain solely of doctors due to the necessity to prescribe and adjust doses of a variety of medicines including phosphate binders and alfacalcidol. The introduction of Patient Group Directions (PGDs) has enabled other health care professionals to gain experience in managing medicines in some specific aspects of their patients' care, for example phosphate management.

A PGD is defined as a written instruction for the sale, supply and administration of named medicines, directly to certain groups of patients (Department of Health, 2000, National Prescribing Centre, 2004). A PGD allows specific allied health care professionals to supply and administer a medicine to a patient, with an identified clinical condition, without the patient first being assessed by a doctor. Pharmacists were one of the professions listed when PGDs were first launched (Department of Health, 2000). In April 2004, dietitians were also authorised to work under PGDs (National Prescribing Centre, 2004).

2.4.2 Patient Group Direction versus Written Protocol

The British Dietetic Association (BDA) (2007) has described the process for developing a PGD or a written protocol and explained the legal aspects associated with dietitians extending their clinical role into drug management. The difference between a PGD and a written protocol can be distinguished by the following guidelines on dose adjustments:

a) A PGD can include dose adjustments provided the drug name and dose range is incorporated into the PGD document, for example patients who need to start taking a drug for the first time. This enables dietitians to work under a legal framework.

b) A written protocol is required if dietitians wish to adjust doses of medications already in the patient's possession, for example stable haemodialysis patients who are already taking phosphate binders or alfacalcidol as in the present study.

The British Dietetic Association (2007) have interpreted this as dietitians being permitted to adjust doses of specific medications prescribed to patients with chronic diseases provided a written protocol has been developed and agreed locally between dietitians and their employers.

2.4.3 Development of a Phosphate Management Protocol

A phosphate management protocol (PMP) was devised within the renal unit at the Barts and the London NHS Trust to enable renal dietitians and renal pharmacists to extend their traditional role in this area of practice. This was developed by the multi-professional renal research team which included a renal consultant, dietitian and pharmacists. The protocol explained in detail which renal clinical staff were involved, the education and training required, the medications and doses included and how the dose adjustments were undertaken safely in a clinical setting (Appendix A2.3). Two algorithms listed which serum biochemistry needed to be checked and action points required if a patient's serum phosphate level fell within or above the target range (Appendices A2.4.1 and A2.4.2). The algorithms were used to inform changes to the dose and type of phosphate binder and the dose of alfacalcidol required to improve patients' serum phosphate, calcium and intact parathyroid hormone (iPTH) levels. The protocol allowed the renal research pharmacists and renal research dietitian, working together, to change patients' medication as specified within the protocol without close supervision of a renal consultant. The protocol was approved by the Barts and The London NHS Trust (BLT) Patient Group Direction Committee.

2.5 Development of the BLT Phosphate Knowledge Questionnaire

2.5.1 Rationale for development

Published questionnaires that have been devised to evaluate patients' self-reported knowledge of adherence to and phosphate management have used a multiple choice question format (Stamatakis et al., 1997, Poduval et al., 2003). These have been used with dialysis patients in North America and included names of food items and phosphate binders which may be unfamiliar to dialysis patients in the United Kingdom. It was, therefore, necessary to design a questionnaire specifically for use with a UK-based haemodialysis study population. Moser et al (1992) describe the general principles of questionnaire design including question content validity, the use of factual or opinion questions and how to avoid ambiguity.

2.5.2 Design of questionnaire

A first draft of the questionnaire, using predominately a multiple choice question (MCQ) format, was designed (Appendix A2.5). It consisted of 19 questions including three on patient demographic information, one question each covering English literacy skills and length of time on dialysis. The remaining questions covered patients' knowledge on current practices in their dialysis unit, self-reported adherence to phosphate binder usage and their dietary phosphate knowledge. Non-adherence was assessed by asking patients how frequently they might omit a phosphate binder dose. To discourage patients from guessing the answers, a "don't know" option was included for some questions.

2.5.3 Pilot of first draft of questionnaire

The questionnaire was piloted on peritoneal dialysis (PD) out-patients at St. Bartholomew's Hospital, London. These patients were studied as they receive the same phosphate binder medications and low phosphate diet education as haemodialysis patients and would be expected to have similar levels of phosphate knowledge when tested but were not eligible to participate in the main study. The pilot study was undertaken over two weeks in two PD out-patient clinics. The patients were supervised by one of the study researchers. Each patient was given a copy of the questionnaire to complete in the out-patient waiting area. The majority of patients were able to complete the questionnaire, with minimal or no assistance from the researcher. However, in three cases the questionnaire was only completed with help from the researcher. The findings from the pilot study enabled ambigious and confusing questions to be identified. Demographic data (i.e.

gender, nationality, age) of the PD patients who participated and their responses were expressed as percentages of the total pilot population.

2.5.4 Revised questionnaire

The diet section of the first questionnaire included food items rich in both phosphate and potassium for example milk, chocolate and nuts. During diet consultations, with renal patients, there is often a tendency for them to name foods rich in potassium when, in fact, low phosphate diet advice is required. This frequent observation suggests that patients can get confused about what food contains in relation to their renal diet. Therefore, when designing the questionnaire, the concern with using a MCQ format was that patients may choose a correct answer by mistake, which could have resulted in false correct answers. If this were to occur then the questionnaire would not have accurately tested patients' phosphate knowledge. Consequently, the findings from the pilot study helped identify ambiguous and confusing questions and informed changes to the question format in order for the questionnaire to evaluate only the patients' phosphate knowledge. The final questionnaire consisted of eleven questions. Open questions were mainly used to ascertain patients' knowledge on phosphate management issues (Appendix A2.6). To discourage patients from guessing the answers, a "don't know" option was included for some questions. It was decided that the study patients would be interviewed by one of the researchers, as this would help control the time allocated to this part of the consultation.

2.5.5 Questionnaire validity and reliability

The aim of this process was to ensure that the revised questionnaire had content validity. The topics included in the revised questionnaire were discussed and agreed by the renal research team which comprised a dietitian, pharmacists and a consultant nephrologist. The questionnaire was completed twice, by five haemodialysis patients who did not participate in the study, in order to assess test-retest reliability. On the first occasion, patients were asked the questions in the questionnaire by the researcher in a face-to-face interview. On the second occasion, the same researcher telephoned the patient at home and repeated the same questions. The test-retest reliability of the revised phosphate knowledge questionnaire was examined using the method described by Bland and Altman (1986). A Bland and Altman plot was drawn to examine the size of the score differences and their distribution around zero by plotting the mean knowledge score for each patient on the X axis and the change in their score on the Y axis. Limits of agreement were defined as mean score difference ± 2 standard deviations. The lower and upper lines of agreement are also

shown on the Bland-Altman plot (Figure 4.5). Questionnaire development and assessment will be discussed in more detail in chapters 3 and 5.

2.5.6 Questionnaire Scoring

Patients' responses to the questions about current phosphate management practices on their units (i.e. were they kept informed about their serum phosphate level) did not contribute to the questionnaire score. Responses to knowledge questions were classified as correct or incorrect according to predetermined criteria. One point was awarded for every correct answer and zero points for a wrong answer or a "don't know". The total maximum score possible was 30 points (Appendix A 2.6).

Chapter 3: METHODS

3.1 Participants

3.1.1 *Recruitment*

The patients studied were recruited from adult outpatients with chronic kidney disease undergoing regular haemodialysis (three times per week) during daytime sessions at Barts and the London NHS Trust (BLT) between June 2003 and September 2003. Inclusion criteria were age over 18 years, clinically stable, English speakers, mentally alert and at least one elevated serum phosphate level > 1.8mmol/l during the proceeding 4 months. Patients who met these criteria were invited to participate in the study. Patients who did not speak English, and those with patients with malignancy, gastrointestinal disorders including malabsorption, planned surgery, visual or hearing difficulties which impaired their routine communication with healthcare professionals were excluded from the study.

Patients who fitted the study criteria, agreed to participate and provided informed written consent were randomised into one of two study groups using a computer generated random number list:

a) Phosphate management protocol (PMP) group

b) Standard practice (SP) group

All study patients, in both groups, were reviewed and blood results monitored once per month for the 4-month duration of the study.

3.2 Renal Dietetic Input

At each monthly visit, all patients were seen individually by a renal dietitian who devised an individual care plan. The individual dietary advice was given after taking a diet history (Bingham 1987) and comprised verbal advice supported by either a detailed low phosphate diet booklet providing a comprehensive list of high-phosphate foods to avoid and suitable alternatives, or a simplified handwritten diet action plan. A copy of 1st line low phosphate diet sheet can be found in the appendices (Appendix A3.1). The choice of written material was based on each patient's circumstances and their perceived ability to understand the instructions given. Patients were advised whilst they were undergoing haemodialysis. During the study, the PMP group were seen by the renal research dietitian and the SP group by the HD unit dietitian.

3.3 Intervention

3.3.1 Phosphate Management Protocol Group

Monthly blood samples were taken from each patient and analysed in the same laboratory at BLT with the exception of the serum aluminium samples which were sent to the Clinical Chemistry department at Liverpool University Hospital. Results were accessed via the BLT renal database. The research renal dietitian and pharmacists discussed the results of patients in the PMP group on a monthly basis. Adjustments to the type and dose of phosphate binders and the dose of alfacalcidol prescribed were agreed by the dietitian and pharmacists, using the PMP and algorithms and then confirmed by the renal consultant (Appendices A2.4.1 and A2.4.2). The renal research pharmacists explained to the patients, whilst they were undergoing haemodialysis, about the changes to their medication, counselled them about when to take them and the adjustments required in relation to the size of their meals and provided a medication card (Appendix A3.2). The renal consultant was informed about any patients whose serum biochemistry required a medical referral, as stated in the algorithms (Appendices A2.4.1 and A2.4.2).

3.3.2 Standard Practice Group

In the SP group, a senior doctor within the renal team reviewed the monthly blood results and adjusted the dose and type of phosphate binder and the dose of alfacalcidol during dialysis wards rounds or at an outpatient clinic. The renal research team pharmacist and research dietitian did not advise these patients and they were not seen by the renal research dietitian but received the standard dietetic management as described in section 3.2.

3.4 Data Collected

The following patient information was collected:-

a) Demographic data (age, gender and racial group).
b) Clinical data (aetiology of kidney disease, length of time since commencing haemodialysis and adequacy of dialysis).
c) Nutritional data (weight, height).
d) Serum biochemistry (phosphate, corrected calcium, iPTH and aluminium).
e) Phosphate medication
f) Phosphate knowledge

Table 3.1 summarises the data collected and the relevant timepoints when each variable was collected during the study.

Table 3.1

Summary of the data collection throughout the main study for all patients (n = 34).

Variables						
	Recruitment	Baseline				End of Study
Time period		Month 0	Month 1	Month 2	Month 3	Month 4
Demographics						
Age (years)	X					
Gender	X					
Racial group	X					
Clinical						
Aetiology of kidney disease	X					
Length of time on haemodialysis (years)	X					
Adequacy of dialysis (Kt/V)	X					X
Nutritional						
Weight (kg)	X	X	X	X	X	X
BMI (kg/m^2)	X					X
Serum Biochemistry						
Phosphate (mmol/l)	X	X	X	X	X	X
Corrected calcium (mmol/l)	X	X	X	X	X	X
Intact parathyroid hormone (pmol/l)	X	X				X
Calciumxphosphate product ($mmol^2/l^2$)	X	X	X	X	X	X
Aluminium (μmol/l)		X				X
Phosphate Information						
Medication		X				X
Knowledge	X	X				X

3.4.1 Details of data collections

Clinical data

Adequacy of haemodialysis was assessed by second generation logarithmic estimates of single-pool variable volume, Kt/V for each study patient (Daugirdas 1993). Kt/V is defined as the fractional clearance of urea and was estimated by using the following equation:

$$Kt/V = \text{Natural Logarithm } \ln(R - 0.008 \times t) + 4 - (3.5 \times R) \times \frac{UF}{W}$$

where R = Ratio of the postdialysis serum urea ÷ predialysis serum urea

T = Length of a single haemodialysis session (hours)

UF = Ultrafiltrate volume (litres)

W = Body weight after dialysis weight (kg)

Nutritional data

Weight was measured using either standing scales (Tanita BWB-600, Yiewsley, UK) or for patients who could not stand, sitting scales (WeighCare, Looe, UK). Patients were weighed wearing light clothing and without outdoor footwear, pre and post each dialysis session. BMI is a ratio of weight divided by height squared (kg/m^2). For the purpose of this study BMI was calculated from body weight divided by height squared using previously recorded heights. The study patients' were weighed after HD which is known as the "dry" weight as it is expected that excess fluid has been removed during the HD session. The "dry" weight is determined by a renal doctor undertaking a physical assessment to establish the fluid status, for each patient. Fluid status can be sub-divided into three categories i) fluid overload, ii) in fluid balance (euvolaemic) and iii) dehydrated (Daugirdas 2001).

Serum biochemistry

Routine blood samples were taken from all study patients before haemodialysis within the first week of the month. Serum was separated and frozen within one hour of blood collection so that accurate measurements could be made of iPTH levels. Serum phosphate and corrected calcium concentrations were analysed using ultraviolet and colour photometric tests respectively (Smith et al., 1998, Thomas 1998).

Serum corrected calcium levels were adjusted with reference to serum albumin:
Corrected calcium (mmol/l) = measured calcium (mmol/l)+([40 – albumin (g/l)]x 0.02)
(Falk et al., 1997)

Calcium-phosphate product was calculated by multiplying serum phosphate and corrected calcium levels.

Serum iPTH and aluminium concentrations were measured at the beginning and end of the study by an automated chemiluminescent immunoassay and atomic absorption spectrophotometry respectively (Godber et al., 2002, Roberts et al., 1998).

Phosphate medication

The phosphate binders and dose prescribed to study patients were also recorded. Phosphate binders are classified according to their chemical composition, British National Formulary (2008):

a) Calcium carbonate: Calcichew® (Shire, Basingstoke, UK), Calcium-500 (Martindale, Brentwood,UK) and Titralac® (3M, Bracknell, UK)
b) Calcium acetate: Phosex® (Vitaline, Aylesbury, UK)
c) Aluminium hydroxide: Alu-Cap® (3M, Bracknell, UK)
d) Sevelemer hydrochloride: Renagel® (Genzyme, Cambridge, USA)

Phosphate knowledge

The revised phosphate knowledge questionnaire was administered to all patients in both PMP group and SP groups, at baseline and at the end of the 4-month intervention period. The questionnaire was administered to each study patient, whilst they were undergoing haemodialysis, by either a renal research pharmacist or renal research dietitian who read out the questions to the patient and recorded the answers. The researchers visited the participating dialysis units and all of the study patients dialysing at the same unit, were tested on the same day. The same researcher interviewed the same patients throughout the study period for consistency. The researchers aimed to standardise the interview process by not deviating from the words used on the questionnaire. The maximum time taken to complete each patient interview was fifteen minutes.

3.5 Statistical Analysis

3.5.1 Statistical Power

Power calculations undertaken, for the original study design, indicated that a sample size of 17 patients in each group was required to detect a 15% reduction in serum phosphate levels (80% power at a significance level of 0.05).

The power calculation was undertaken retrospectively, for the final study design. To detect a reduction in serum phosphate level from 2.16 to 1.80 mmol/l (difference = 0.36mmol/l) with 80% power at 0.05 level of significance, 15 patients were required in each study group.

Both power calculations were based on data from an audit of BLT haemodialysis patients in 2000.

3.5.2 Statistical tests

The distribution of variables were tested for normality using the Shapiro-Wilks' test because the study population was less than 100 subjects (SAS 8.2, 2001, SAS Institute Inc, Cary, USA). The remaining data were analysed using the statistical package (Systat 10.2, 2002, Systat Software UK Limited, Hounslow,UK).

In the main study, descriptive statistics were calculated for all variables. The mean and standard deviation were calculated for normally distributed data (age, most nutritional and biochemical variables and phosphate knowledge scores). The median and range were used to describe data not normally distributed (time on dialysis and iPTH levels). Interquartile ranges, which are 25^{th} and 75^{th} percentile values, were also quoted for iPTH levels. The change in serum phosphate levels was calculated by subtracting pre-intervention levels from post intervention levels for both groups. A negative value indicated an improvement in the post intervention result whereas a positive value indicated a deterioration. The same calculation was carried out for phosphate knowledge scores, in this case a positive value indicated an improvement in the post intervention knowledge. The pre and post intervention phosphate knowledge questionnaires were analysed only.

Statistical comparisons were made between the two patient groups at recruitment, baseline and post-intervention using unpaired t tests for normally distributed data and Mann Whitney U tests for data not normally distributed. The difference between baseline and post-intervention results within each group were compared using paired t tests and Wilcoxon matched pairs test for normally distributed and not normally distributed data

respectively. The difference between the change from baseline to post-intervention in the two groups were compared using unpaired t-tests and Mann Whitney U tests. Chi-squared test was used to compare proportions of categorical data between the two groups, e.g. for comparing the male to female ratio in the two study groups.

McNemar's test was used to compare the proportions of patients who achieved individual target values for serum phosphate, corrected calcium, CaxP product and iPTH and answered phosphate knowledge questions correctly within each group before and after intervention. Cochran's test for linear trend was used to compare the proportions of patients who achieved multiple serum biochemical targets within each group at baseline and post intervention.

Linear regression was performed to determine whether there was a significant relationship between the change in serum phosphate level (dependent variable) and change in phosphate knowledge score (independent variable). A backwards stepwise multivariable linear regression analysis was performed to determine whether any of the independent variables (study group, age, gender and time on dialysis) were independent predictors of the change in serum phosphate level. Non-significant variables were subtracted from the model one at a time until only significant variables were left in the model.

Statistical significance was defined at the 20% level, i.e. P values less than 0.05.

3.6 Ethical Considerations

3.6.1 Informed consent

Patients who met the study inclusion criteria were invited to participate by one of the researchers during one of their haemodialysis sessions. The study was explained and patients who were interested were given a patient information leaflet (Appendix A3.3) to read at home. Patients were encouraged to discuss the study with their relatives before making a decision. This was followed by a conversation, between the patient and one of the researchers, either on the dialysis unit or by telephone and for those verbally agreeing to participate, signed informed consent was obtained at their next visit (Appendix A3.4).

3.6.2 Confidentiality

Each patient received a unique code number and this was used to ensure anonymity throughout the study. A list of patient names and corresponding unique code numbers were

kept in locked files in the secure offices at the Royal London Hospital in accordance with the Data Protection Act 1998 (Appendix A3.5).

3.6.3 Continuity of Care

In order to ensure that patients received optimum care and that their treatment followed the PMP and SP pathways according to their randomization, all professional staff at each of the participating dialysis centres were informed about the study. The general practitioner of each participating patient was also informed about the study (Appendix A3.6).

Patients were not paid to participate in this study.

Ethical approval was granted by the North East London Strategic Health Authority (NELSHA) Research Ethics Committee, reference number P/01/092 (see Appendix A2.1).

Chapter 4: RESULTS

4.1 Subjects

4.1.1 Recruitment

Serum phosphate levels were monitored for four consecutive months. Fifty-eight patients were identified as having at least one value > 1.8mmol/l during this period. Twelve patients declined to participate, two patients were not adequately dialysed, which was defined as Kt/V < 1.2, and therefore did not meet the inclusion criteria and two patients died. The 42 remaining patients who consented to participate were randomised to one of the two intervention groups; 34 of these received the interventions and 31 patients completed the study. Five patients in the PMP group and three patients in the SP group did not receive the interventions, (Figure 4.1). At recruitment, the two groups were comparable in terms of age, gender, racial group, aetiology of kidney disease, length of time since commencing regular haemodialysis and BMI (Table 4.1).

4.1.2 Patients who did not complete the study

Three patients, two men and one woman, received the intervention but did not complete the study. Two of the patients were White British and the other was Black Caribbean. The underlying aetiology of their renal disease was glomerulonephritis in two cases and hypertension for the third patient and all three patients were allocated to the PMP group. Two patients were withdrawn in week 6 after developing complicated or confounding medical conditions (total parathyroidectomy for severe hyperparathyroidism and oropharyngeal squamous cell carcinoma requiring feeding via a gastrostomy) and the third died from septicaemia secondary to endocarditis in week 9. The data from these patients were included in the comparative analysis at recruitment (Table 4.1) but not in subsequent analyses. This is in accordance with the post randomisation exclusion intention to treat principle as described by Fergusson et al (2002) whereby excluding these patients from further analysis was acceptable due to the fact that they did not complete the full 4-month intervention period.

A statistical comparison of the clinical and nutritional data was undertaken between the three patients who were withdrawn and all of the remaining patients, in both study groups, who completed the study (Table 4.2). No statistically significant differences were observed between these two groups with the exception of serum iPTH levels with median (range) values higher in the three withdrawn patients at recruitment than in the remaining patients who completed the study, 157 (135-178) vs 38 (0.3-181), P=0.05).

Figure 4.1

Flow of participants through trial

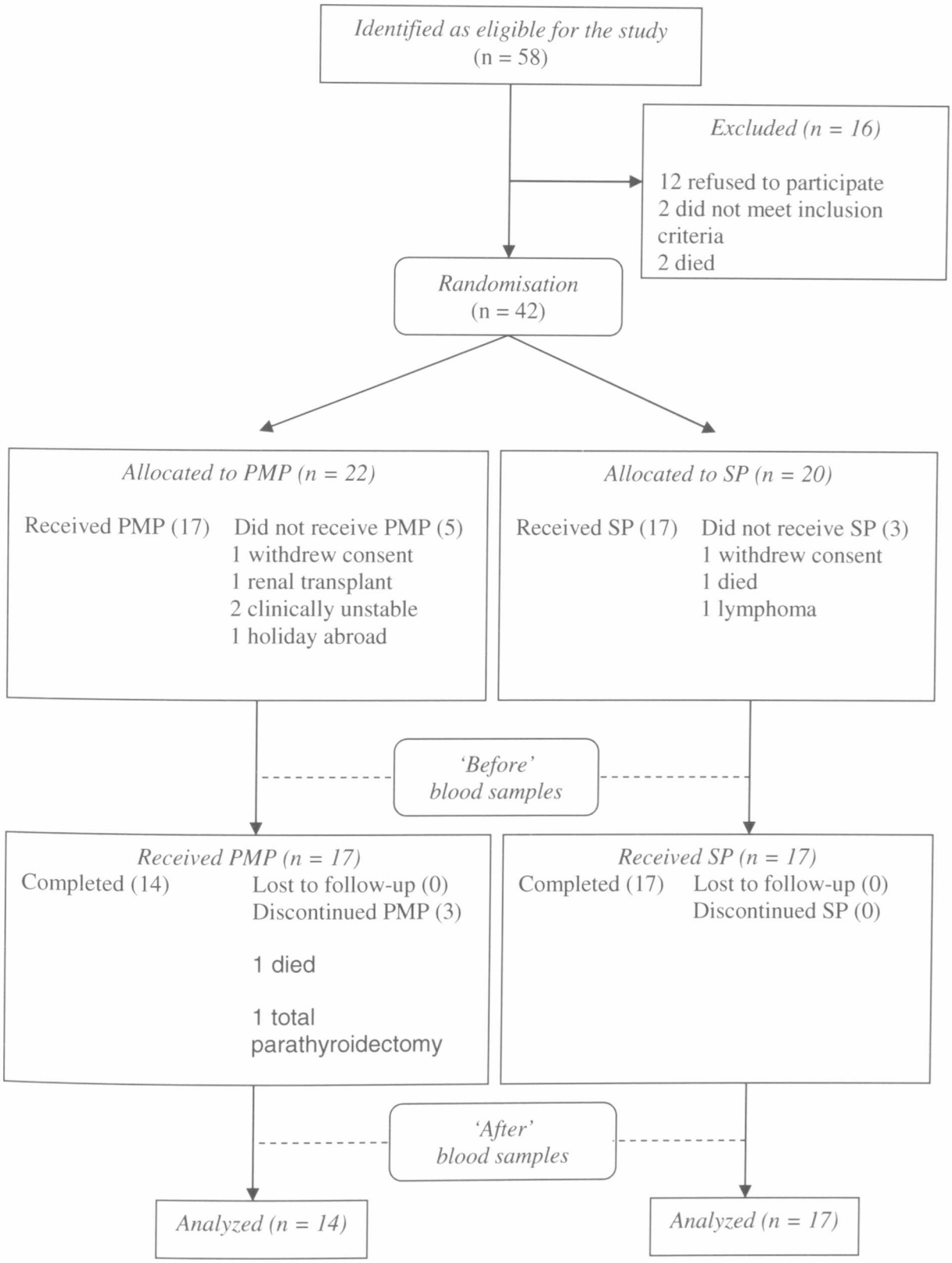


Table 4.1

Demographic, clinical and nutritional characteristics of the 34 randomised patients at recruitment. Values are expressed as mean ± SD except where indicated

	Phosphate management protocol group (n = 17)	Standard practice group (n = 17)	P value
Age (years)	51.1 ± 12.7	47.6 ± 14.4	0.46
Male : female ratio (n)	11M : 6F	12M : 5F	0.71
Racial group			
Black	5	4	
Indoasian	1	2	
White	11	10	
Other	0	1	
Aetiology (n)			
Glomerulonephritis	5	2	
Diabetes	3	2	
Hypertension	2	3	
Adult polycystic kidneys	1	2	
Pyelonephritis	0	2	
Unknown	2	2	
Other[a]	4	4	
Length of time on HD[b] (years)	2.0 (<1 – 10)	2.5 (<1 – 7)	0.5
Nutrition			
Height (m)	1.71 ± 0.10	1.66 ± 0.10	0.13
Weight (kg)	71.1 ± 15.8	71.7 ± 13.1	0.90
BMI (kg/m^2)	24.3 ± 4.8	26.3 ± 5.5	0.27

[a]Include focal segmental glomerulosclerosis, IgA nephropathy, oxalosis, tuberculosis, Goodpasture's syndrome

[b]Median (range)

4.2 Serum Biochemistry

4.2.1 Summary of serum results at baseline

No statistically significant difference was observed in serum phosphate concentrations, corrected calcium or iPTH levels between the two groups before the study intervention. However, Ca x P product was significantly higher in the PMP group than in the SP group at this time point (5.01 ± 0.74mmol^2/l^2 vs 4.38 ± 0.86 mmol^2/l^2, P=0.04) (Table 4.3).

Serum phosphate levels after intervention

After the intervention, PMP group showed a small, insignificant reduction whilst a significant increase in serum phosphate was observed in the SP group. The mean serum phosphate level achieved, post intervention, by the PMP group was 1.81mmol/l which is

Table 4.2

Clinical and nutritional comparison of PMP group patients who withdrew and all of the remaining study patients (PMP and SP)

Values are expressed as mean ± SD except where indicated

Parameters	PMP patients withdrawn (n = 3)	Patients who completed the Study (n =31)	P value
Age (years)	45.3 ± 0.6	49.7 ± 14.1	0.59
Time on HD[a] (years)	2 (<1 – 4)	2.25 (<1 - 10)	0.47
Serum phosphate (mmol/l)	2.08±0.28	2.41 ± 0.45	0.22
Serum corrected calcium (mmol/l)	2.42 ± 0.09	2.34 ± 0.30	0.63
Serum Ca x P product ($mmol^2/l^2$)	5.04±0.81	5.58 ± 1.03	0.39
Serum iPTH[a] (pmol/l)	157(135 – 178)	38 (0.3 – 181)	0.05
Weight (kg)	60.6 ± 8.1	72.5 ± 14.4	0.17
BMI (kg/m^2)	22.1 ± 1.0	25.6 ± 5.3	0.26

[a] median (range)

equivalent to the upper end of the target range (Tables 1.4 and 4.3). The results showed that patients managed using the phosphate management protocol achieved a significant reduction in the mean change in serum phosphate levels compared to patients receiving standard practice (-0.22 ± 0.67mmol/l, t= -1.23 vs +0.19 ± 0.32mmol/l, t= +2.46, P = 0.03).

Serum corrected calcium levels after intervention

Mean serum corrected calcium levels were stable for both study groups, throughout the study period (Table 4.3). However, after the intervention, the mean serum corrected calcium levels for the PMP group were higher than for SP group (Table 4.3) and were also outside the target range of 2.10 – 2.37mmol/l, set by NKF (2004), (Table 1.4). Whereas, for the same time period, the SP group achieved and maintained mean serum corrected

Table 4.3

Effect of phosphate management protocol and standard practice on biochemical variables in patients undergoing regular haemodialysis (mean ± 1SD except where stated).

	Phosphate management protocol (n=14)				Standard practice (n=17)				Intergroup	Intergroup
	Before	After	Change	Intragroup P value	Before	After	Change	Intragroup P value	P value Before	P value Change
Serum phosphate (mmol/l)	2.03±0.28	1.81±0.54	-0.22±0.67	0.24	1.88±0.32	2.07±0.25	+0.19±0.32	0.03	0.18	0.03
Corrected calcium (mmol/l)	2.48±0.26	2.47±0.15	-0.01±0.28	0.95	2.34±0.26	2.34±0.26	0±0.16	0.92	0.15	0.91
Ca x P ($mmol^2/l^2$)	5.01±0.74	4.43±1.20	-0.58±1.62	0.20	4.38±0.86	4.80±0.51	+0.41±0.81	0.05	0.04	0.04
iPTH[a] (range) [IQR][b] (pmol/l)	36 (0.3-224) [10,87]	51 (0.3-175) [11,66]	-2 (-75 to 40) [-24,+4]	0.38	29 (0.3-237) [10,148]	21 (0.3-165) [8,85]	0 (-214 to 26) [-33,11]	0.64	0.85	0.89

[a]median (range)

[b][interquartile range]

calcium levels within the target range (NKF 2004), (Table 1.4). There were no significant differences in the change in serum corrected calcium levels, both within and between the study groups (Table 4.3).

Calcium-phosphate product after intervention

The mean CaxP product achieved, post intervention, by the PMP group was 4.43mmol^2/l^2 which is equivalent to the upper end of the target range (NKF 2004), (Table 1.4). Parallel differences, to those obtained for mean serum phosphate levels, were observed in the mean change in Ca x P product between the two groups after intervention (-0.58 ± 1.62mmol^2/l^2, t= -1.34 vs +0.41 ± 0.81mmol^2/l^2, t= +2.10, P =0.04) (Table 4.3).

Serum intact PTH levels after intervention

For the PMP group, the median serum iPTH level increased to 51 pmol/l which was outside the target range of 16.0 - 33.0, set by NKF (2004), (Table 1.4). Whereas, for the SP group, the median serum iPTH level decreased to 21 pmol/l and this group managed to achieve and maintain median serum iPTH levels within the target range (NKF 2004), (Table 1.4). The median change achieved in iPTH levels by PMP and SP groups were -2pmol/l and 0pmol/l respectively. There was no significant difference in the median change in iPTH levels between study groups, after intervention (Table 4.3). The implications of some study patients having iPTH levels exceeding the 75th percentile will be discussed in chapter 5.

Serum aluminium levels after intervention

Only one patient (SP group) had an elevated serum aluminium level before the intervention (2.6 µmol/l) (NKF 2004), (Table 1.4). This responded to reducing her dose of Alucaps (3M, Bracknell, UK). In all other patients, aluminium levels remained within acceptable limits throughout the study.

Haemodialysis adequacy

Mean haemodialysis adequacy, as indicated by Kt/V, was comparable between the two groups at recruitment (PMP 1.30 ± 0.25 vs SP 1.32 ± 0.17, P=0.77) and at the end of the study (PMP 1.29 ± 0.29 vs SP 1.43 ± 0.20, P=0.14). These results have demonstrated that the majority of haemodialysis patients can be adequately dialysed, as defined by NKF (1998) and described in chapter one section 1.6.5.

Nutritional variables

Nutritional status as evaluated by BMI remained comparable in both groups throughout the study.

Table 4.4

Effect of phosphate management protocol and standard practice on patients achieving individual K/DOQI targets. NKF (2004)

K/DOQI targets for serum variables		Number (%) of patients with serum variable within target [Trend]		P value
		Before	After	
PO_4 (1.13-1.80 mmol/l)	PMP (n=14)	2 (14)	5 (36) [↑]	0.08
	SP (n=17)	7 (41)	3 (18) [↓]	0.10
Corrected calcium (2.1-2.37 mmol/l)	PMP (n=14)	5 (36)	4 (29) [↓]	0.56
	SP (n=17)	7 (41)	5 (29) [↓]	0.41
Ca x P product (<4.44 $mmol^2/l^2$)	PMP (n=14)	3 (21)	7 (50) [↑]	0.16
	SP (n=17)	10 (59)	5 (29) [↓]	0.06
iPTH (16.0-33.0 pmol/l)	PMP (n=14)	1 (7)	1 (7) [↔]	1.00
	SP (n=17)	2 (12)	4 (24) [↑]	0.32

Comparisons undertaken using a McNemar test

4.3 Achieving National Kidney Foundation: Kidney Dialysis Outcome Quality Initiative Targets

The McNemar test has been used to compare the proportions of patients who achieved the K/DOQI serum targets, within the same study group. The proportion of patients achieving the K/DOQI targets increased in the PMP group and decreased in the SP group for serum phosphate and CaxP product levels following the intervention period. Whereas only the SP

group improved their iPTH levels after intervention (Table 4.4). Any changes observed were not significant within groups (Table 4.4). Chi square tests were also undertaken to compare the proportions of patients, between the study groups, who achieved the K/DOQI serum targets at baseline and after the intervention. Only CaxP product was found to be statistically different between groups, at baseline with values of 3 (21%) and 10 (59%), P= 0.04 for PMP and SP groups respectively.

Similarly, the proportion of patients meeting multiple K/DOQI targets improved in the PMP and decreased in the SP group, on comparing the number of patients who achieved two or three K/DOQI serum targets. However these trends were also not significant within groups. It must be noted that none of the study patients, in either groups, achieved four K/DOQI targets (Figures 4.2 i and ii).

4.4 Phosphate Binders

4.4.1 Binder Usage

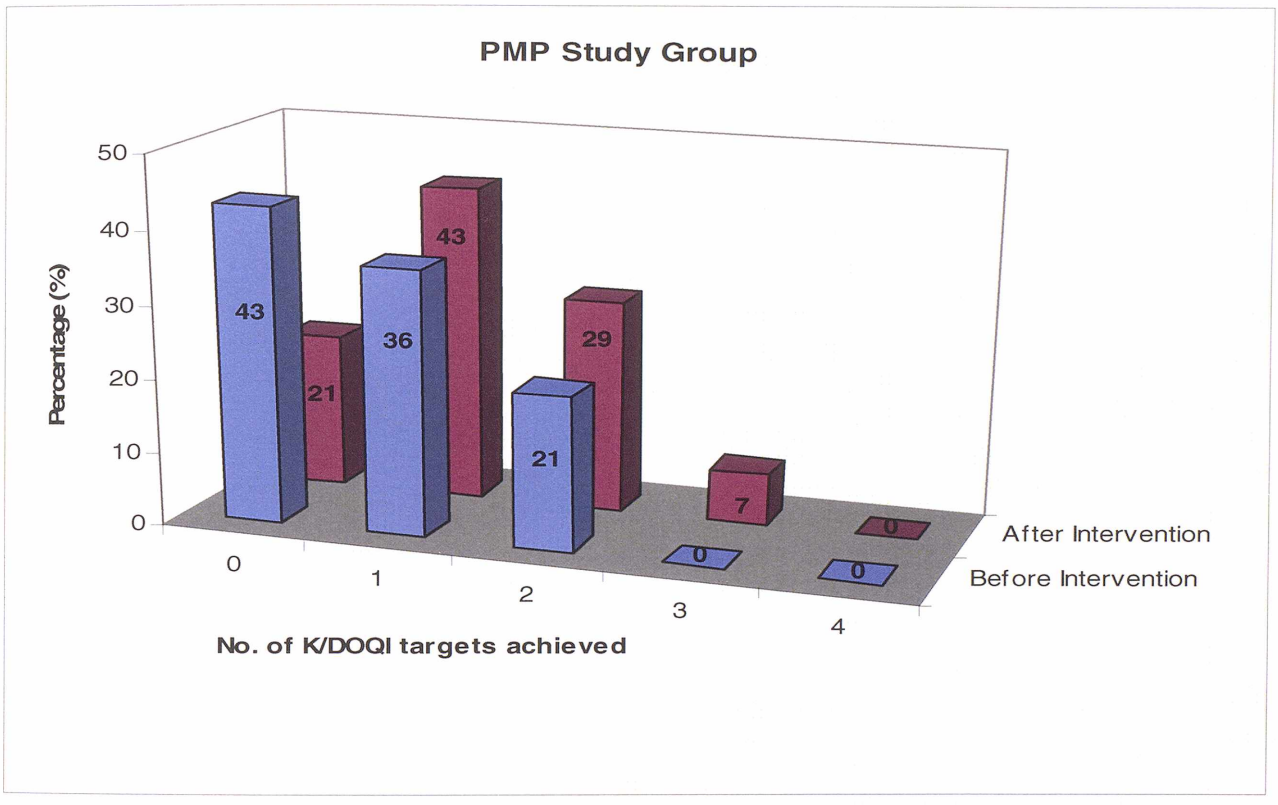
All of the patients in the PMP group took phosphate binders throughout the study compared to 16 (94%) of the patients in the SP group. Figure 4.3 demonstrates the variety of phosphate binders prescribed for patients in this trust. The number of patients taking phosphate binders, in both groups, did not change after the intervention. Before the intervention, the number of patients taking two different types of binders concurrently was four (29%) and eight (50%) for PMP and SP groups respectively. At the end of the study, the number of patients taking two different binders rose to seven (50%) in the PMP group whilst in the SP group the number remained unchanged.

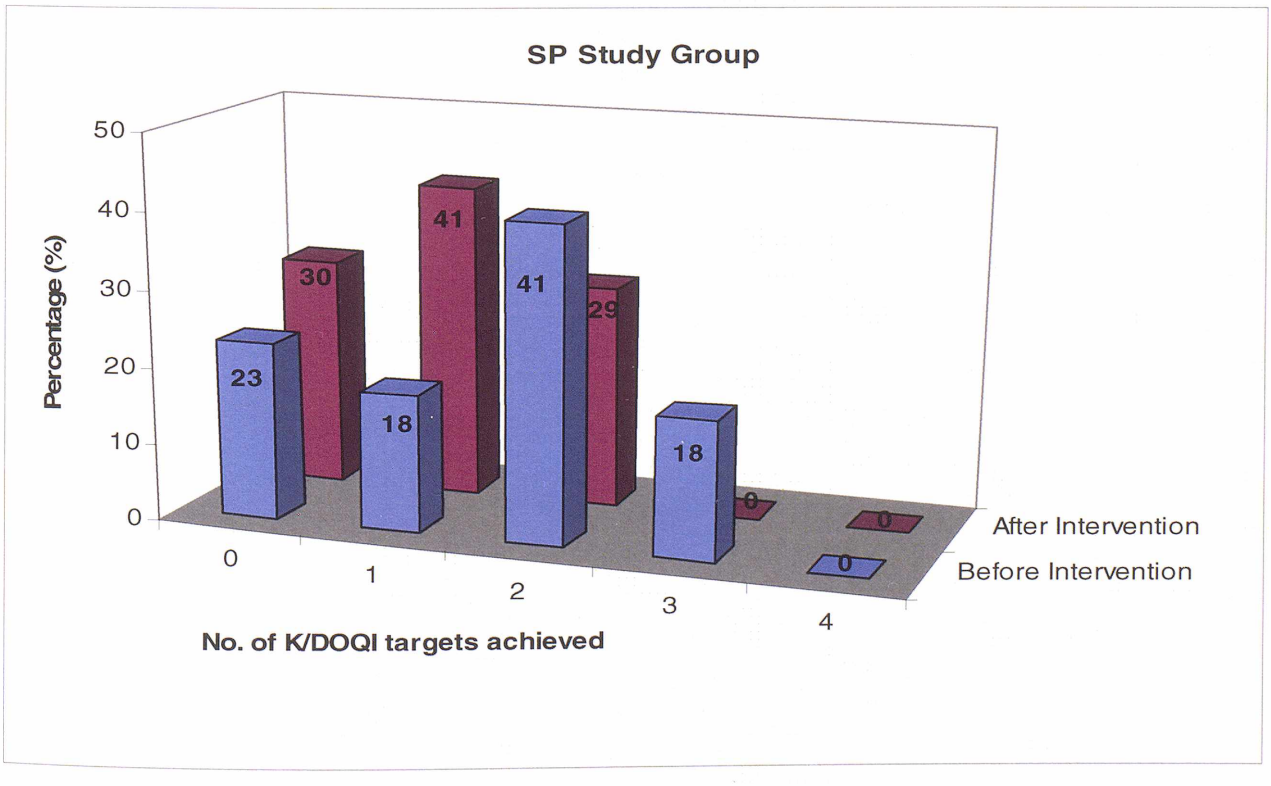
4.4.2 Dose Adjustments

Significantly more changes to the dose of phosphate binders were made in the PMP group than in the SP group (median [range] number of dose changes, PMP 5 [1-7] vs SP 0 [0-3], ($P<0.001$). It should be noted that for some patients, a change in dose was required in more than one phosphate binder at each occasion.

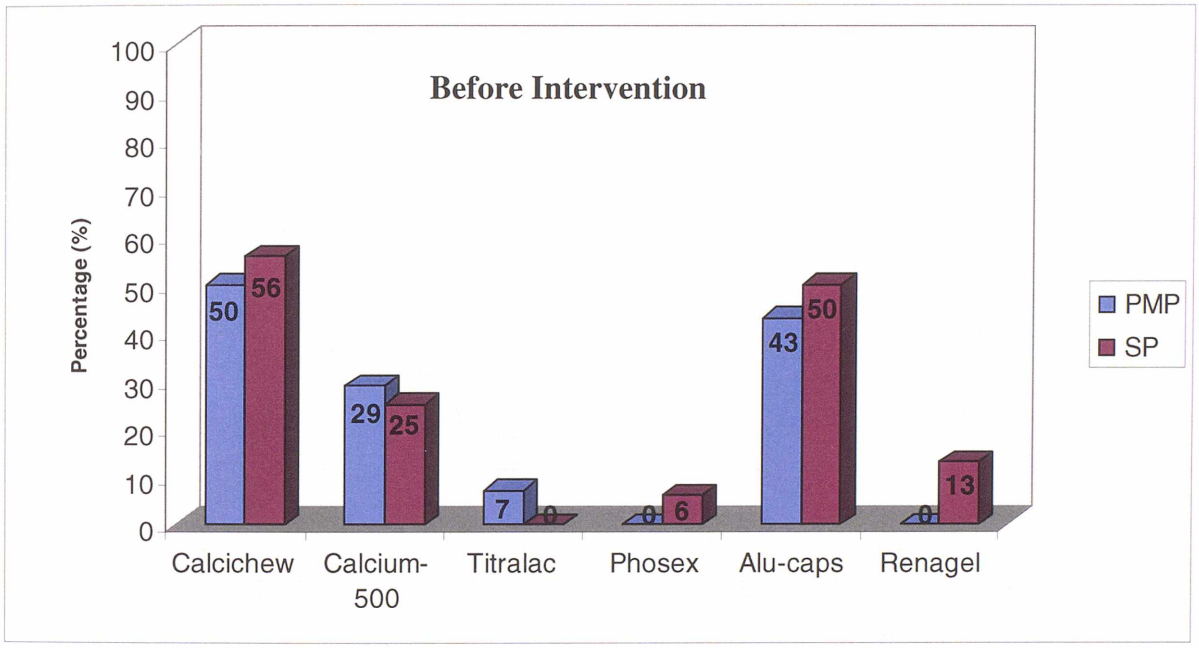
4.4.3 Reported Compliance

Eighty-six percent of PMP patients and 88% of SP group patients reported they took their binders as advised 10 minutes or less before their meals. The frequency of adherence to phosphate binder prescription reported by patients are summarised in Figure 4.4).

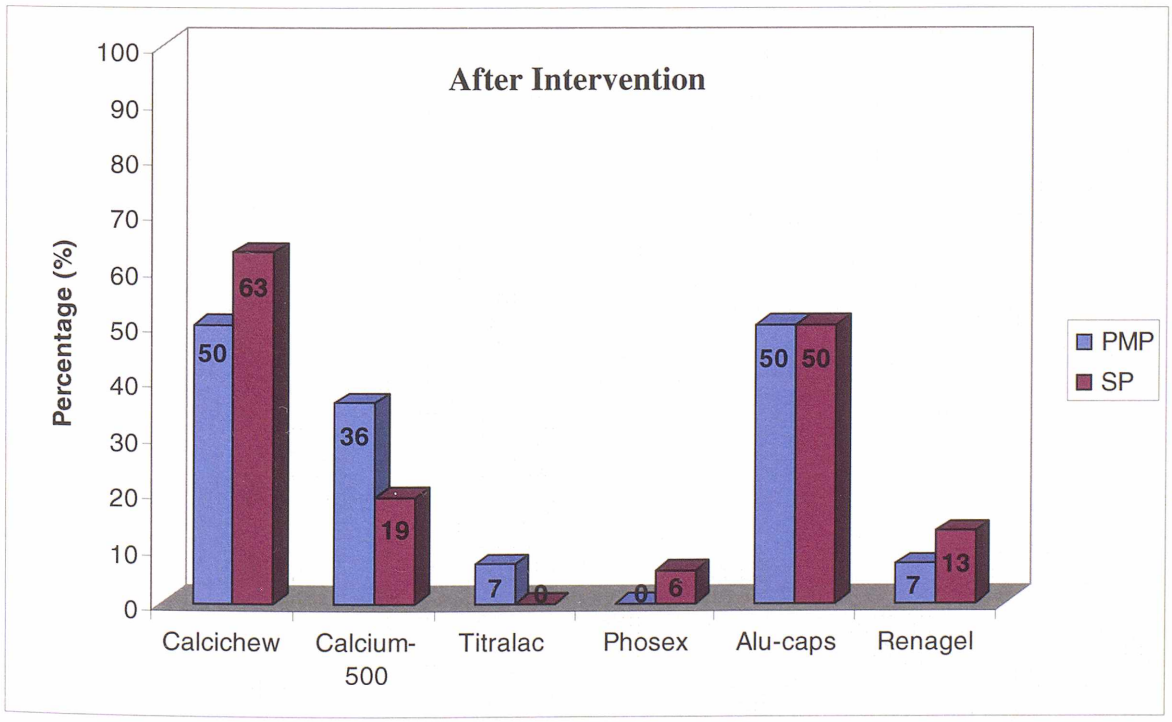




Figures 4.2 (i) and (ii) Effect of phosphate management protocol and standard practice on patients achieving multiple K/DOQI targets (NKF 2004).

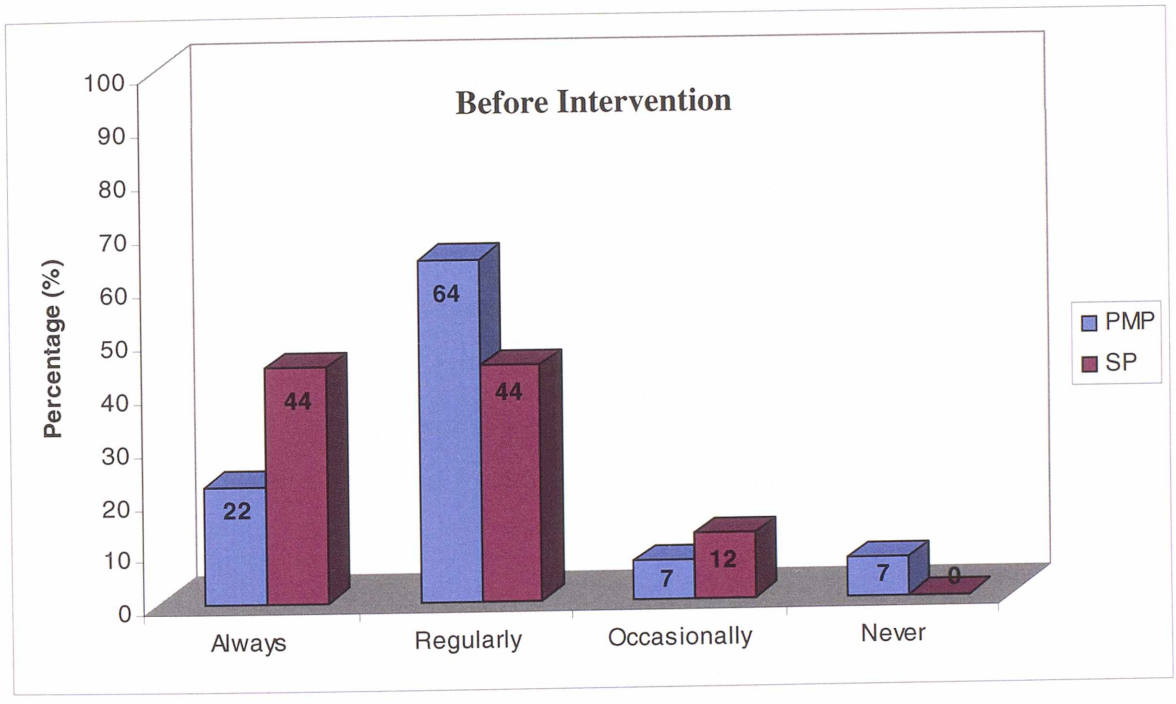


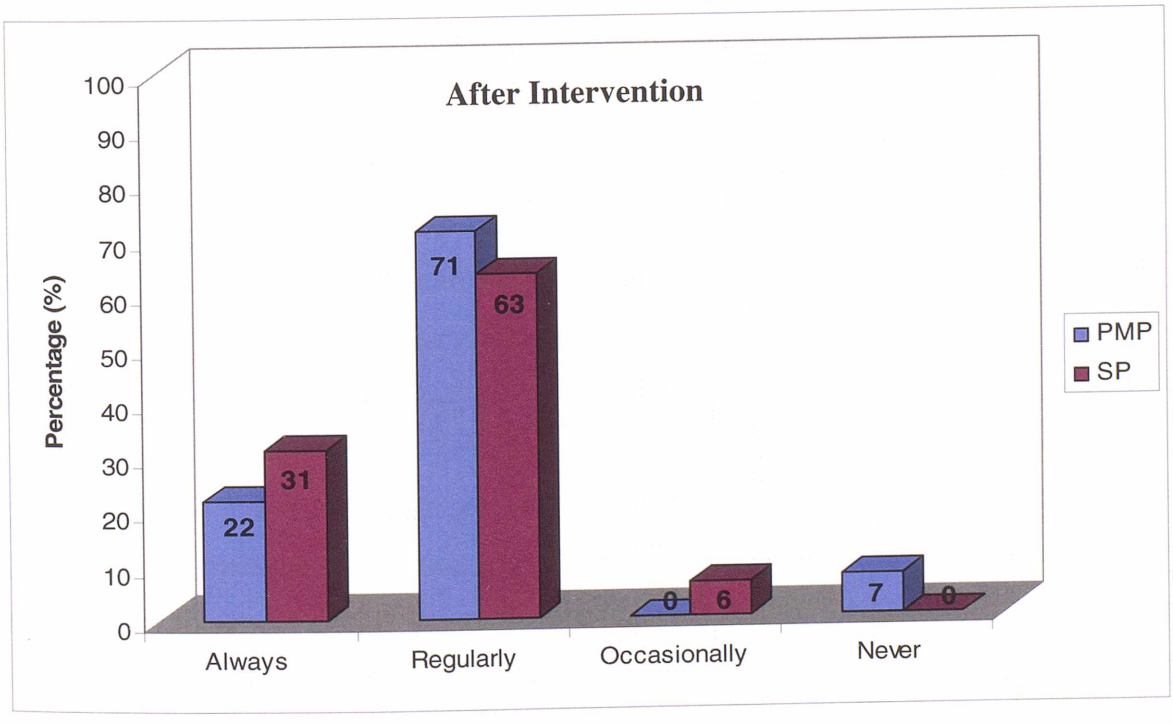
ii)



Figures 4.3 (i and ii)

The types of phosphate binders haemodialysis patients in both study groups were taking, in the main study, before and after the intervention (results are expressed as percentages)





Figures 4.4 (i and ii)

Responses obtained from haemodialysis patients in both study groups, in the main study, before and after intervention, to the question "On average do you take your binders as prescribed?" (Results are expressed as percentages).

4.5 Patients' Contact Time with Pharmacists and Dietitians

Each month, for each PMP patient only, the pharmacists recorded the time they spent undertaking face-to-face contact and patient related activities, on patient data collection forms. The mean time spent with patients by the pharmacists in the PMP group was 19 [8-25] minutes per month whereas patients in the SP group were not seen by the pharmacists. The renal dietitian also spent additional time discussing the patients' blood results and formulating treatment plans with the renal pharmacist, whereas monthly dietetic reviews, for patients at each HD site, was routine clinical practice. The renal research dietitian did not collate time and motion data to quantify the additional time spent on patient related activities.

4.6 Breaches to Protocol

Eight breaches of the study protocol occurred during the study relating to physicians changing binders between monthly reviews without reference to the protocol in the PMP group. On each occasion, when the breach was identified by the pharmacist, the serum levels were reviewed promptly against the protocol and an appropriate amendment made in compliance with the protocol.

4.7 Phosphate Knowledge Questionnaire Pilot

4.7.1 Pilot Study Patient Population and Responses

The pilot study patient population was comparable in terms of age and racial group to the main study patient population. The only difference was in the length of time on dialysis as the majority of the pilot study patients (i.e. on peritoneal dialysis) had only been on dialysis for one year or less compared to the main study population whose average time on haemodialysis was two years. A summary of the PD patients responses to the questionnaire were compiled (Appendix 4.1).

4.8 Revised Phosphate Knowledge Questionnaire

4.8.1 Questionnaire Reliability

Five haemodialysis patients, who did not participate in the study, completed the revised phosphate knowledge questionnaire twice with an interval of one week. The two sets of scores obtained were very similar and are presented in a Bland-Altman plot Figure 4.5. The plotted spread of results did not show any systematic pattern and the change in knowledge scores were within the mean difference ± 2SD. Consequently, the changes were not deemed to be clinically relevant and thus the questionnaire considered reliable in

this patient population. It must be noted that on-retesting one patient achieved a score three points more than on initial testing. It is feasible that this patient referred to information, previously received, prior to the re-test to ensure a higher score was achieved.

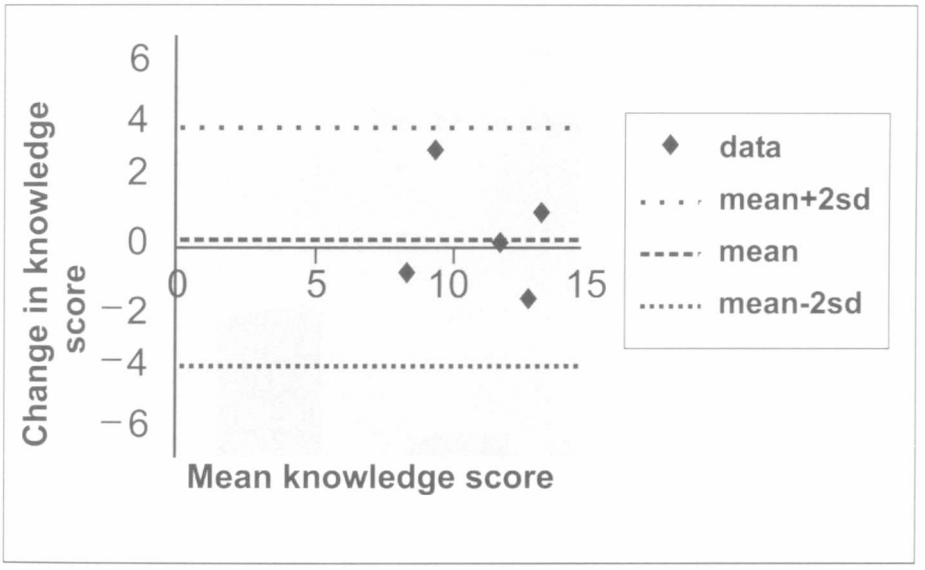


Figure 4.5 Bland-Altman plot demonstrating the reliability of the revised phosphate knowledge questionnaire.

4.8.2 Patients' Knowledge of Current Phosphate Management Practices

In the main study population, both before and after intervention, more SP patients stated that they were informed by HD staff about their blood phosphate level each month. All other responses were comparable between groups (Figure 4.6). Approximately 40-50% of patients in both groups reported that they asked HD staff what their blood phosphate level was each month (Figure 4.7).

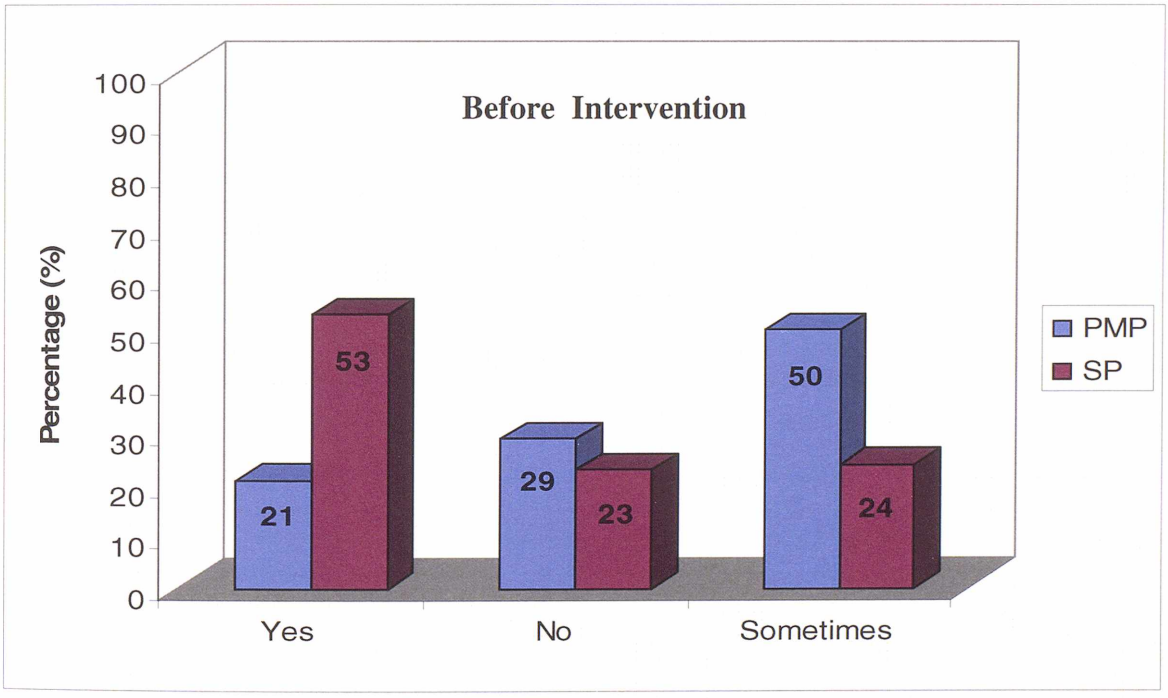
4.8.3 Testing Patients' Phosphate Knowledge of haemodialysis patients

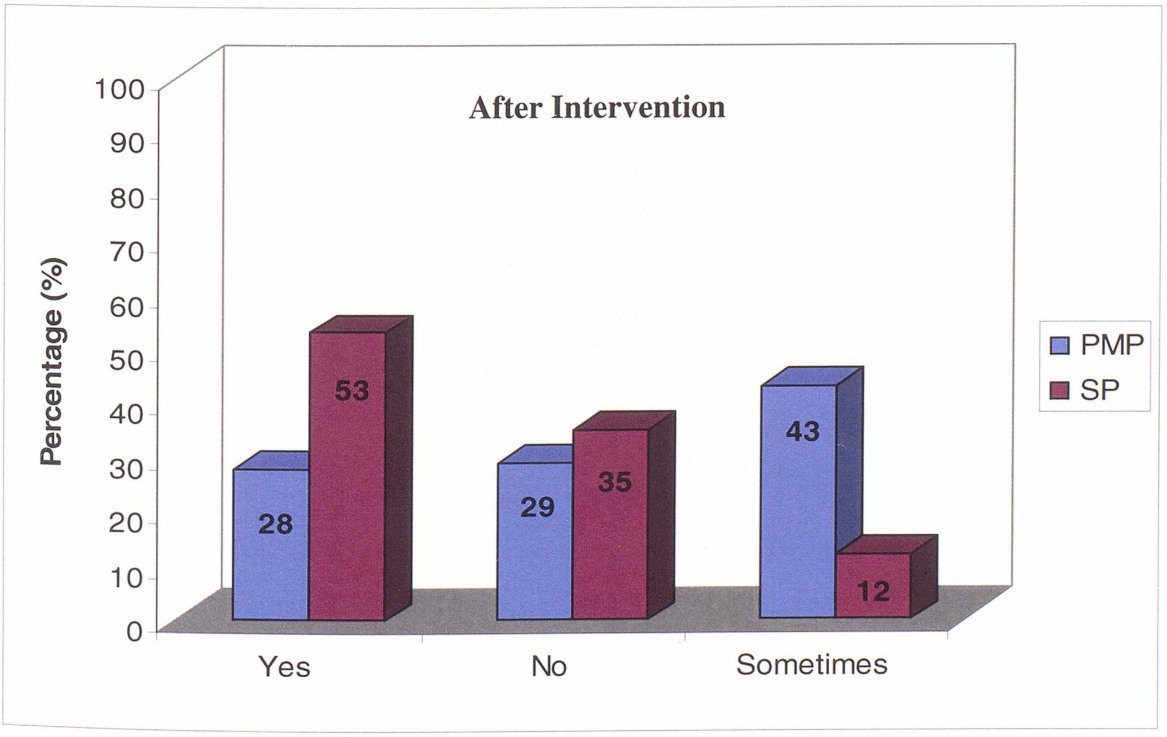
i) Total score

The total score, that a patient could achieve, was 30 points. Since the mean score was approximately 15 points for both study groups, both pre-and post-intervention this is equivalent to 50% of the answers being correct (Table 4.5). The results of the study patients' phosphate knowledge are summarised in Tables 4.6 - 4.10).

No statistical difference was observed in the phosphate knowledge scores between the two groups at the start of the study (Table 4.5). A comparison of the mean change in knowledge scores, between the groups over the study period, did not show a significant improvement in the PMP group compared to the patients in the SP group

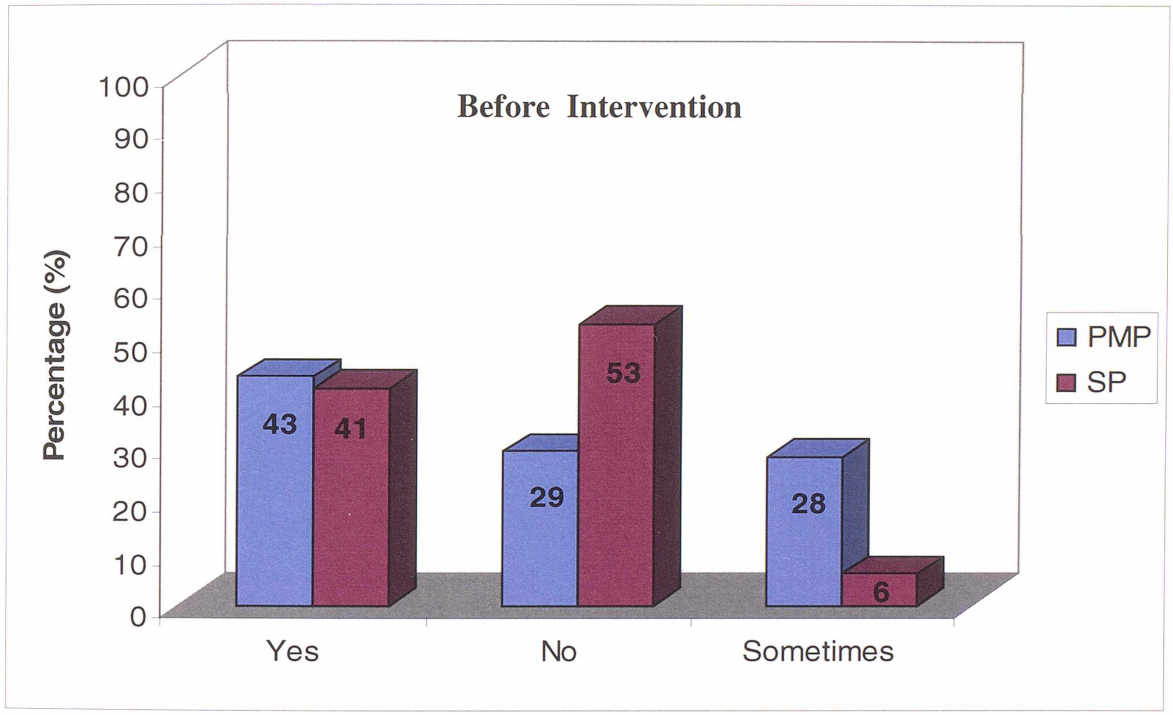
(-0.79±3.33, t= -0.88 vs -0.12±2.45, t= -0.20, P =0.53). No significant differences were observed between the proportions of patients providing correct answers to phosphate knowledge questions within each group following intervention (Tables 4.6 - 4.10).

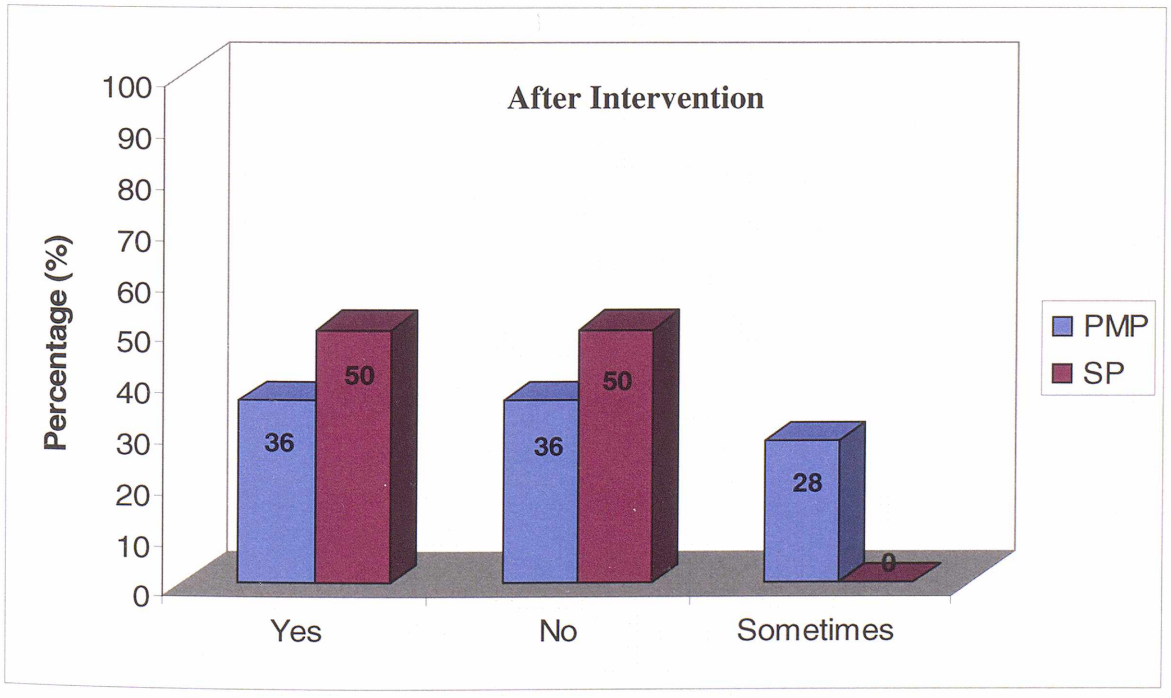




Figures 4.6 (i and ii)

Responses obtained from haemodialysis patients in both study groups, in the main study, before and after intervention, to the question "Are you told what your blood phosphate level is each month?" (Results are expressed as percentages).





Figures 4.7 (i and ii)

Responses obtained from haemodialysis patients in both study groups, in the main study, before and after intervention, to the question "Do you ask the staff what your blood phosphate level is each month?" (Results are expressed as percentages.)

Table 4.5

Effect of phosphate management protocol and standard practice on phosphate knowledge scores for patients undergoing regular haemodialysis (mean ± 1SD)

	Phosphate management protocol (n=14)				Standard practice (n=17)				Intergroup P value Before	Intergroup P value Change
	Before	After	Change	Intragroup P value	Before	After	Change	Intragroup P value		
Phosphate Knowledge Score	15.5±3.6	14.7±3.3	-0.8±3.3	0.39	14.1±3.9	13.9±4.4	-0.1±2.5	0.85	0.29	0.53

Comparisons undertaken using paired and unpaired t-tests

ii) A summary of the phosphate knowledge results

More PMP group patients knew the target blood phosphate level compared to patients in the SP group both before or after intervention (Table 4.7).

The proportion of study patients, in both groups, who were able to state that itchy skin was a symptom of high serum phosphate levels was greater than 60%. All of the PMP group provided the correct answer to this question before the intervention but two PMP patients were unable to recall this information at the end of the study. For the SP group one additional patient knew the correct answer after the intervention (Table 4.7). Less than 30% of study patients, in both groups, knew that red eyes were a symptom of hyperphosphataemia (Table 4.7).

The majority of patients were aware of the long term effect that hyperphosphataemia has on the bones. More PMP group patients knew this compared to patients in the SP group (Table 4.8). A trend suggesting an improvement in patients' knowledge was observed post intervention, in the PMP group only, but this was not statistically significant (Table 4.8).

Other parts of the body affected by persistent hyperphosphataemia were less well known (Table 4.8). For example, less than 50% of the patients, in both groups, named the heart as a correct answer. Fewer patients, less than 20% in both groups, were aware that skin were also affected long term. None of the patients, pre-intervention, knew blood vessels were affected and only one SP patient, provided the correct answer at the end of the study (Table 4.8).

Finally, more than 60% of patients in both groups knew that phosphate binders and a low phosphate diet were treatments to correct hyperphosphataemia (Table 4.6). Whereas less than 40% of patients, in both study groups, were aware that haemodialysis also has a role in lowering serum phosphate levels (Table 4.7).

iii) Dietary phosphate knowledge

Tables 4.9 and 4.10 summarises the results of the patients' dietary phosphate knowledge. More than 50% of all study patients, both pre and post intervention, were able to identify phosphate rich foods which should be avoided (Table 4.9). More than 60% of all study patients, both pre and post intervention, knew the foods rich in phosphate which could be included in their diet, in limited quantities (Table 4.10).

Table 4.6

Effect of phosphate management protocol and standard practice on patients providing the correct phosphate knowledge answers

Phosphate Knowledge Questions		Number (%) of patients who gave the correct answers		P value
		Before	After	
Do you know how your blood phosphate level can be controlled? **Answer: Diet**	PMP (n=14)	12 (86)	10 (71)	0.32
	SP (n=17)	15 (88)	12 (71)	0.08
Do you know how your blood phosphate level can be controlled? **Answer: Binders**	PMP (n=14)	10 (71)	9 (64)	0.56
	SP (n=17)	13 (76)	12 (71)	0.70

Table 4.7

Effect of phosphate management protocol and standard practice on patients providing the correct phosphate knowledge answers (contd)

Phosphate Knowledge Questions		Number (%) of patients who gave the correct answers		P value
		Before	After	
Do you know what blood phosphate level should be? **Answer: 0.8-1.8mmol/l**	PMP (n=14)	4 (29)	6 (43)	0.16
	SP (n=17)	1 (6)	2 (12)	0.32
What symptoms might you experience if you have a high phosphate level? **Answer: Red Eyes**	PMP (n=14)	4 (29)	3 (21)	0.32
	SP (n=17)	4 (24)	3 (18)	0.32
What symptoms might you experience if you have a high phosphate level? **Answer: Itchy skin**	PMP (n=14)	14 (100)*	12 (86)	*
	SP (n=17)	11 (65)	12 (71)	0.66
Do you know how your blood phosphate level can be controlled? **Answer: Dialysis**	PMP (n=14)	5 (36)	3 (21)	0.32
	SP (n=17)	0 (0) §	1 (6)	§

Comparisons undertaken using a McNemar test

* P value was not calculated since PMP group achieved 100% correct answers before intervention therefore a 2x2 table was not feasible

§ P value was not calculated since none of the patients answered this question correctly therefore a 2x2 table was not feasible

Table 4.8

Effect of phosphate management protocol and standard practice on patients providing the correct phosphate knowledge answers (contd)

Phosphate Knowledge Questions		Number (%) of patients who gave the correct answers		P value
		Before	After	
Do you know which parts of your body can be affected by poor blood phosphate control in the long term? **Answer 1: Heart**	PMP (n=14)	6 (43)	5 (36)	0.32
	SP (n=17)	1 (6)	1 (6)	1.00
Answer 2: Skin	PMP (n=14)	2 (14)	2 (14)	1.00
	SP (n=17)	1 (6)	0 (0) [§]	[§]
Answer 3: Bones	PMP (n=14)	10 (71)	12 (14)	0.32
	SP (n=17)	9 (53)	9 (53)	1.00
Answer 4: Blood Vessels	PMP (n=14)	0 (0) [§]	0 (0) [§]	[§]
	SP (n=17)	0 (0) [§]	1 (6)	[§]

Comparisons undertaken using a McNemar test

[§] P value was not calculated since none of the patients answered this question correctly therefore a 2x2 table was not feasible

Table 4.9
Effect of phosphate management protocol and standard practice on patients providing the correct phosphate knowledge answers (contd)

Phosphate Knowledge Questions		Number (%) of patients who gave the correct answers		P value
		Before	After	
Which food item should be avoided as part of a low phosphate diet? **Answer 1: Muesli**	PMP (n=14)	6 (43)	7 (50)	0.66
	SP (n=17)	10 (59)	8 (47)	0.32
Answer 2: Liver	PMP (n=14)	10 (71)	8 (57)	0.16
	SP (n=17)	9 (53)	10 (59)	0.32
Answer 3: Nuts (as a snack)	PMP (n=14)	13 (93)	12 (86)	0.32
	SP (n=17)	15 (88)	13 (76)	0.16
Answer 4: Fish with soft edible bones	PMP (n=14)	9 (64)	8 (57)	0.32
	SP (n=17)	10 (59)	11 (65)	0.32
Answer 5: Ovaltine	PMP (n=14)	11 (79)	8 (14)	0.08
	SP (n=17)	14 (82)	12 (71)	0.32

Comparisons undertaken using a McNemar test

Table 4.10

Effect of phosphate management protocol and standard practice on patients providing the correct phosphate knowledge answers (contd)

Phosphate Knowledge Questions		Number (%) of patients who gave the correct answers		P value
		Before	After	
Which food items are allowed in moderation as part of a low phosphate diet?	PMP (n=14)	10 (71)	10 (71)	1.00
Answer 1: Cheese	SP (n=17)	11 (65)	11 (65)	1.00
Answer 2: Yogurt	PMP (n=14)	9 (64)	13 (93)	0.08
	SP (n=17)	11 (65)	11 (65)	1.00
Answer 3: Milk	PMP (n=14)	13 (93)	13 (93)	1.00
	SP (n=17)	17 (100)*	15 (88)	*

Comparisons undertaken using a McNemar test

* P value was not calculated since SP group achieved 100% correct answers before intervention therefore a 2x2 table was not feasible

4.9 Relationships Between Variables

4.9.1 Single Variable Linear Regression

Single variable linear regression analysis was undertaken using change in serum phosphate as the dependent variable (Table 4.11). The variable study group, accounted for a significant 14.7% of the variation in the change in serum phosphate level (P=0.03), whereas female gender and change in knowledge score accounted for 6.3% and 2.8% respectively. The remaining two independent variables included in the analysis (i.e. age and time on dialysis) both accounted for 1.2% of the variation in the change in serum phosphate level but neither were statistically significant. In total, these variables accounted for 26.2% of the variation in the change in serum phosphate level

An equation was formulated using the data obtained from single variable analysis which is shown in Table 4.11. By using this equation the change in serum phosphate level (dependent variable) could be predicted for both study groups:-

Change in serum phosphate (mmol/l)

= constant coefficient + 0.408 (study group)

= -0.22 + 0.408 (study group)

= - 0.227 + 0* (for PMP group) **or** + 0.408 (for SP group)

*For regression analysis PMP and SP groups were coded zero (0) and one (1) respectively.

Therefore predicted change in serum phosphate level for :-

i) **PMP group = -0.22 + 0 = -0.22mmol/l**

ii) SP group = -0.22 + 0.408 = +0.188mmol/l

These results compare to those obtained and summarised in Table 4.3.

4.9.2 Multi-Variable Linear Regression

Relationship between serum phosphate and all variables

None of the independent variables (i.e. age, gender, time on haemodialysis and change in knowledge score) were found to be statistically significant when the multiple linear regression analysis was undertaken. Study group was marginally significant (P = 0.055) and in total, the variables accounted for 21.7% of the variation in the change in serum phosphate level. Since this further analysis did not provide any useful additional information, only the results of the single variable linear regression have been presented in detail.

Table 4.11

Single linear regression: Relationships between variables in the main study (n =31)

Variable	Coefficient	Std Error	P value	r^2
Constant	-0.220	0.135	0.033	0.147
Study group	0.408	0.182		
Constant	0.017	0.098	0.372	0.028
Change in Knowledge Score	0.031	0.035		
Constant	0.211	0.364	0.560	0.012
Age	-0.004	0.007		
Constant	-0.070	0.160	0.565	0.012
Time on HD	0.002	0.003		
Constant	0.095	0.116	0.175	0.063
Gender	-0.283	0.204		

In the next chapter, the results of this study will be discussed and compared to those reported by other researchers, who have conducted similar studies. The current study will be critiqued and ideas for future studies will be also discussed.

Chapter 5: DISCUSSION

In this chapter the results, of the current study will be discussed in relation to recruitment and retention of the study patients, effectiveness of the phosphate management protocol and the evaluation of patients' self-reported adherence to phosphate binders and phosphate knowledge and with respect to the published literature.

5.1 Discussion of results

5.1.1 Recruitment and retention

Despite an approximate total of 220 patients dialysing at four BLT haemodialysis units the initial target to recruit 68 study patients was not achieved (Figure 4.1). This was mainly due to the communication problems with the haemodialysis population, some of whom were unable to speak English. Since the inclusion criteria stipulated that all study patients must be English speakers this meant that the number of potential patients was reduced. However the racial demographic data, in table 4.1, shows that almost 60% and 30% of the patients in both study groups were white and black respectively. Therefore, the proportion of patients who should speak English were in the majority. The recruitment period was restricted to 4 consecutive months due to time constraints, associated with the funding of the study by BLT Research and Development department. Problems commonly associated with recruiting and retaining study patients were experienced, for example twelve patients declined to participate and after randomization two patients withdrew their consent (Figure 4.1). Durose et al (2004) also reported a similar number of patients who declined to participate and acknowledged that by not collecting demographic data on these patients it was not possible to determine whether their omission from the study may have introduced bias. A similar assumption may be linked to this study.

Retention issues more specific to renal studies, were experienced in this study whereby one patient, in the PMP group, received a cadaveric kidney transplant prior to the start of the intervention. In comparison, the study undertaken by Ashurst et al (2003) reported of patients who underwent a kidney transplantation post intervention, therefore enabling these patients results to be included in data analysis. To eliminate any differences between the two study groups at recruitment a randomised controlled study design was used. Table 4.1 indicates that the randomisation process was effective despite five and three patients, randomised to the PMP and SP groups respectively, did not receive the assigned treatments.

Intention to treat principle

The comparison between the three patients who had to withdraw, from the PMP group, and all of the remaining patients who completed the study demonstrates that there were no statistically significant differences between these groups demographic data except for a borderline significant difference in median (range) serum iPTH levels of 157 (135 – 178)pmol/l and 38 (0.3 – 181)pmol/l, P=0.05 respectively (Table 4.2).

At the time this study was undertaken patients with iPTH levels > 80pmol/l were more at risk of being referred to the renal surgeons for a surgical parathyroidectomy, based on the assumption that medical management had been unsuccessful (National Kidney Foundation 2004). At recruitment, the median and inter-quartile ranges of iPTH levels, for PMP and SP groups, were 66pmol/l (6.4,135) and 18 pmol/l (9.4,120) respectively. The fact that some patients, in both study groups, with severe SHPT levels, fell within the 50% distribution category, highlights how controlling this parameter in hyperphosphataemic patients is another challenge for renal healthcare professionals. The results, shown in table 4.4, for achieving the K/DOQI iPTH level target also confirm this to be true. Based on the iPTH levels observed, in this current study, there was a potential risk of losing more patients to parathyroidectomies.

It could argued that these outliers, belonged to a subgroup, on the basis of their elevated iPTH levels. However these patients were valid participants, for this current study, as elevated serum phosphate levels stimulates the parathyroid gland to release iPTH into the blood. If the PMP intervention was effective and lower serum phosphate levels were achieved then reduced iPTH levels, as a secondary outcome measure, should have been observed also.

Although two of the three patients were still alive at the end of the study the treatments they both received would have had a significant effect on the serum biochemistry which were relevant to this study. The female patient would have been prescribed high doses of alfacalcidol (4 micrograms) and elemental calcium (3000mg) pre-parathyroidectomy (PTX). Post-operative close monitoring of serum levels would have been necessary as transient hypocalcaemia requiring parenteral calcium supplements may sometimes occur. Alternatively, enteral calcium and vitamin D supplementation would have been continued (Rashed et al., 2004).

Significant decreases in serum phosphate and corrected calcium levels have been reported on the first day post PTX (Jovanovic et al., 2005). In view of the radical medical

management required both pre and post PTX and the changes in relevant serum biochemistry post PTX it would not have been appropriate to include end of study blood results for this patient.

This male patient, who was diagnosed with oropharyngeal squamous cell carcinoma underwent a percutaneous endoscopic gastrostomy (PEG) tube insertion. The enteral tube feed used was Nepro® which is specially formulated for renal patients therefore it is low in phosphate. To meet the patient's daily nutritional requirements 750ml of Nepro provided 1500kcal, 53grams protein and 518mg phosphate. When compared to the recommended daily intake of 1000mg phosphate this specialist feed, formulated for patients with electrolyte and fluid restrictions, contained 50% less dietary phosphate. It is most likely that this patient's serum phosphate and iPTH levels would have fallen spontaneously therefore including further data from this patient would not have been suitable.

In summary, the post randomisation exclusion intention to treat principle as described by Fergusson et al (2002) was correctly applied in these circumstances due to the fact that the three study patients did not complete the full 4-month intervention period and they were no longer stable HD patients post withdrawal.

5.1.2 Phosphate management protocol

Serum biochemistry levels and analysis

i) Serum phosphate levels

The results from the current study suggests that the use of a defined phosphate management protocol, by experienced renal pharmacists and a renal dietitian for four consecutive months, was able to achieve a small insignificant reduction in serum phosphate levels in the PMP group. However the statistically significant difference in the mean change in serum phosphate level observed, post intervention, could be explained by the increase in the mean serum phosphate level of the SP group.

To enable the trust committee to grant authorisation for the PMP to be used as the treatment intervention for this study the research staff involved had to be experienced renal healthcare professionals with the relevant background knowledge in phosphate management and necessary skills to carry out the tasks required. Therefore, the reduction in serum phosphate level achieved by the PMP group may be due to the research team

being more effective at counselling the patients on making the relevant changes to their diet and medications during the four month intervention period.

Although a number of studies have evaluated the effects of single elements of managing hyperphosphataemia, including dietary counselling and education (Prowant et al., 1989, Stamatakis et al., 1997, Schlatter et al., 1998, Ashurst et al., 2003, Ford et al., 2004) and pharmacotherapy (McIntyre et al., 2002) few have investigated an algorithm-based protocol for the management of hyperphosphataemia (Craven et al., 1996, Johnson et al., 2002, Casey et al., 2006). In addition to the studies mentioned above, and discussed in detail in chapter one, two other relevant research studies were published while this study was being undertaken (Durose et al., 2004, Ford et al., 2004).

The study by Ford et al (2004) yielded results broadly similar to this study. They conducted a randomised control study using 63 HD patients. At recruitment, all patients had a serum phosphate level greater than 1.94mmol/l. Patients in the intervention group received approximately 30 minutes of individual diet counselling for six consecutive months, by a renal dietitian. They found that patients who received the intensive education achieved a significant reduction in their serum phosphate level when compared to the control group. Post intervention, the serum phosphate levels were 1.68±0.39mmol/l and 2.16±0.55mmol/l, P=0.0001 for the intervention and control groups respectively. The trends in serum phosphate levels achieved by both groups, post intervention were similar to those obtained in this current study. It should be noted that the intervention group in this study was able to achieve lower serum phosphate levels in comparison to this current study. This study has used change in serum phosphate level as a main outcome measure for the effectiveness of education however the researchers failed to mention potential confounding factors associated with a change in serum phosphate for example HD adequacy (Kt/V), urine output of patients or changes to phosphate binder doses (Karamanidou et al., 2008). Unless the researchers ensured no changes were made to the study patients' HD dose or medication regimes during the intervention period then the results reported must be treated with caution. The issue of confounding variables affecting serum phosphate control will be discussed later in this chapter. Ford et al (2004) also tested patients' knowledge both pre- and post intervention, which can be directly associated with education. Since this study was able to recruit and retain sufficient patients to achieve robust statistically significant results the change in phosphate knowledge post intervention should yield worthwhile results. These will be discussed later in this chapter.

In summary, this current study has managed to yield some tentative positive results, by using a phosphate management protocol, in a HD patient population.

ii) Serum corrected calcium levels

The maintenance of good serum corrected calcium levels, in all of the study patients, demonstrated that this serum variable can be well controlled, despite the use of calcium-based phosphate binders and a vitamin D analogue. Both of which could potentially cause serum calcium levels to rise if close monitoring is not routinely undertaken by experienced renal staff.

iii) Serum calcium-phosphate product

At baseline Ca x P product was significantly higher in the PMP group than in the SP group (Table 4.3). Since these results were the product of the two serum phosphate and calcium levels this indicates that the mean serum levels were lower for the SP group when compared to the PMP group. However it can be stated that the results for the individual mean serum phosphate and calcium levels, compared between groups at baseline, were not statistically significant.

The significance of the actual Ca x P product results could be viewed in relation to the mortality rate data, discussed in chapter 1 (Table 1.7), whereby the PMP group patients with a mean Ca x P product greater than 4.84mmol^2/l^2 indicates that patients in this group had a significantly greater risk of death compared to patients in the SP group, for the same time period.

By the end of the study the mean Ca x P product, for the PMP group was 4.43mmol^{2}l^2, which means that the upper end of the target range was achieved. This value is associated with a lower mortality rate which can be seen as a positive outcome (Table 1.7). In contrast the increase in mean serum phosphate level, observed in the SP group, resulted in a mean CaxP product of 4.80 ± 0.51mmol^2/l^2. However, according to Stevens et al (2004) a mean CaxP product of 4.80mmol^2/l^2 would not have affected these patients' mortality rate (Table 1.7).

iv) Serum intact parathyroid levels

The median change achieved in iPTH levels by PMP and SP groups were -2pmol/l and 0pmol/l respectively. This small decrease achieved by the PMP group may be the beginning of a response to a reduction in serum phosphate levels. However, these results

may indicate that a 4-month monitoring period was insufficient time to detect a significant change in iPTH levels.

Moe et al (2005) conducted a study to compare the effectiveness of a calcimimetic agent, cinacalcet HCl (Sensipar®) and traditional drug therapy including a vitamin D analogue and phosphate binders (control group) for treating SHPT. Since the treatment for the control group was identical to that used in this current study it was therefore useful for the comparison of data. Serum biochemistry levels, including serum phosphate and iPTH levels, were measured at specific time points and the proportion of patients who achieved the K/DOQI targets at baseline and post intervention were assessed. The time period for this study was 26 weeks (6 months) which was two months longer than this current study. The baseline and end of study median (interquartile range) serum phosphate levels for the control group were 2.0 (1.65, 2.3) mmol/l and 1.91 (1.65, 2.16) mmol/l respectively. The baseline and end of study median (interquartile range) serum iPTH levels were 60 (44, 83) pmol/l and 64 (44, 91) pmol/l respectively.These results indicate that six months was also insufficient time to achieve average values for relevant serum parameters within the K/DOQI targets, when using traditional treatments for SHPT. Based on these results, choosing a four month intervention period for the current study was too short a timescale to observe significant changes in serum biochemistry and to demonstrate the effectiveness of PMP alone.

v) Serum aluminium levels after intervention

Serum aluminium levels were monitored both pre and post intervention however, elevated serum aluminium levels were not a concern. This study has demonstrated that Alucaps can be used safely, as a phosphate binder for serum phosphate control, provided they are prescribed inline with clinical guidelines and serum aluminium levels are closely monitored as part of routine clinical practice (National Kidney Foundation 2004).

vi) Haemodialysis adequacy

Monitoring haemodialysis adequacy by calculating urea clearance, Kt/V, is part of the routine standard clinical practice in haemodialysis units (Daugirdas 2001). The target Kt/V is >1.2, for patients receiving haemodialysis three times per week. In this study, the mean Kt/V for both groups achieved the target level both pre-and post-intervention. Therefore, this study has demonstrated that the majority of haemodialysis patients were adequately dialysed, as defined by (National Kidney Foundation 1997) and described in chapter one.

However, it should be noted that due to the kinetics of phosphate clearance, described in chapter one, Kt/V provides an accurate measure of urea not phosphate clearance (Pohlmeier et al., 2001, Kuhlmann 2007). Although maintaining Kt/V > 1.2 may not be a significant confounding variable with respect to improving serum phosphate levels it is deemed as good clinical practice due to its association to mortality rates, previously discussed in chapter one.

Nutritional variables

Provided the patients were euvolaemic and achieved their individual target dry weight then the BMI values calculated would have reflected accurate flesh weights (Daugirdas 2001). BMI data, for both study groups at recruitment, suggest that the patients who participated in the study were likely to be well-nourished and no significant decrease in BMI was observed over the 4-month duration of either arms of the study. Due to the inadequate nutritional data collected in this current study no dietary evidence to support or contradict results published by previous researchers was possible.

Achieving K/DOQI targets after the intervention

In this study trends towards more patients, in the PMP group, achieving these K/DOQI targets were observed after the intervention (Table 4.4). However, the percentage of patients achieving the K/DOQI targets was lower in this study, on comparing with another published study (Tomasello et al., 2004) but more comparable to the end of study results published by Moe et al (2005) (Table 5.1).

These results demonstrate that individual serum biochemistry targets are achievable, with varying success. Interestingly, the one result that was consistent between the studies was the proportion of patients achieving all four targets which was 0% (Table 5.1).

The results of this current study appear to support previous research findings which indicate that achieving both individual and multiple K/DOQI serum targets remain a challenge for haemodialysis patients and renal healthcare professionals.

Table 5.1

Comparison of studies achieving individual and multiple K/DOQI targets

		Study (% patients achieving serum target)			
Serum variables	K/DOQI targets	Tomasello et al (2004)	Moe et al (2005)[$]	Yokum et al (2008)*	
				PMP	SP
Phosphate (mmol/l)	1.13 – 1.8	41	33	36	18
Corrected calcium (mmol/l)	2.1 – 2.37	75	24	29	29
CaxP product ($mmol^2/l^2$)	<4.44	59	36	50	29
iPTH (pmol/l)	16 – 33	35	10	7	24
All 4 targets	(see above)	----	----	0	0

* post intervention results
[$] control group post intervention only

There is a need to determine all of the significant factors which may contribute towards a higher proportion of patients achieving both the serum phosphate target and multiple K/DOQI in the future.

Phosphate Binders

i) Binder usage

An evaluation of phosphate binder usage found that more than 90% of the patients, in both study groups were taking phosphate binders. This result confirms that phosphate binders are used as part of routine serum phosphate management for haemodialysis patients. Data was collected for this study in 2003 – 2004. During this time, the most commonly prescribed phosphate binders were calcium- or aluminium-based. Sevelemer hydrochloride was also available but the prescription rate was low, in both study groups (Figure 4.3). Calcium-containing phosphate binders are associated with progressive cardiovascular calcification (Block et al., 2005). Sevelamer hydrochloride, is both calcium- and

aluminium-free and has been found to be an effective phosphate binder, although gastrointestinal symptoms have been reported (Hervas et al., 2003).

By the end of the study the increased use of two different phosphate binders, as a combination therapy, was observed in the PMP group. It has been speculated that the use of a combination of phosphate binders in a systematic manner, might also reduce the risks associated with individual binders (McIntyre et al., 2002).

ii) Dose adjustments

The significant difference in dose adjustments between the two groups indicates that the PMP group received more interventions, from the renal research pharmacist and dietitian over the 4-month study period. All of the renal consultants in the haemodialysis units from which study patients were recruited, were informed of which group the patients were allocated to. The intention was that the patients in the SP group would continue to receive routine clinical reviews, once the monthly blood results were available, from a renal consultant. The discrepancy in dose adjustments between the study groups is difficult to explain. Recently, BLT renal consultants have conducted various phosphate binder trials, in these cases only the lead consultant was meant to prescribe or alter drug doses, whereas in this current study, HD unit doctors were instructed to continue to review and make necessary changes to phosphate binder and alfacalcidol doses. This issue may highlight a problem recruiting patients from four different HD units, under the care of different doctors, however it also illustrates the importance of clear communication between clinical staff who are directly and indirectly involved with patients participating in studies.

iii) Reported timings for taking phosphate binders

In this study, all patients were surveyed on the time they took their binders in relation to eating their meals. Ten minutes or less before meals, was the correct timing for the aluminium-based binders and most of the calcium-based binders. However the manufacturers' instructions for sevelemer hydrochloride and calcium acetate state that they should be taken with meals. It must be noted that a small number of patients were taking these binders. Therefore, in hindsight, only marking 10 minutes or less as the only correct answer was inappropriate and may have led to an underestimation of the number of patients who were taking their binders at the correct time. It must be noted that Levine et al (1995) investigated whether the timing of calcium based phosphate binder, in relation to mealtimes, had an adverse effect on serum phosphate levels in haemodialysis patients. This study found that the binder could be taken either with or in-between meals and in both cases achieve beneficial effects regarding serum phosphate levels. Despite the results of

this study, now thirteen years old, the advice for patients to take calcium based binders before food still remains. Therefore the interpretation of these particular answers as correct may be of limited clinical significance.

iv) Self reported adherence to phosphate binder prescriptions

Patients were also asked to self-report their adherence to phosphate binders (Figure 4.4). According to these results, more than 80% of patients, in both groups, stated they either never missed a dose or very rarely missed a dose. This level of reported adherence increased to over 90% by the end of the study, for both groups. The accuracy of this result may have to be taken with caution as the question put to patients was phrased "On average do you take your binders as prescribed" which on reflection is too vague and it would have been better to include a time period to add clarity to this question for patients

Self-reported adherence with respect to phosphate binders has been investigated and reported (Tomasello et al., 2004, Karamanidou et al., 2008). Tomasello et al (2004) found that patients took, on average, eight phosphate binder tablets daily. However, the patients who were prescribed the largest number of binder tablets, correlated with patients who had the lowest self-reported adherence. These results indicate that routine clinical practice appears to prescribe more binders in response to persistently elevated serum phosphate levels and it suggests that there is a need to explore if renal unit staff spend time with these patients, or refer them to the renal dietitian, in an attempt to educate them on the medical complications associated with prolonged hyperphosphataemia.

A systematic review has recently been published which attempted to identify the factors associated with non-adherence, specifically in relation to phosphate binder medication (Karamanidou et al., 2008). The authors identified that the method of self reported adherence has its limitations due to the wide range of definitions used. Also patients may feel obliged to report good adherence, especially if they hope to be eligible for a kidney transplant or to ensure that their renal consultant allows them to remain on the transplant list. This review by Karamanidou et al (2008) classified predictors of non-adherence into three categories of variables which were demographic, clinical and psychosocial. Of the demographic variables, in that study, age was routinely found to be strongly associated with adherence. Younger patients were found to adhere less to their phosphate binder regime than the older patients. In this study, the mean age of the study patients was approximately 50 years which may explain the relatively high level of self-reported adherence obtained, based on the results of this review article.

Karamanidou et al (2008) found that none of the clinical variables were found to be strongly associated with binder adherence. However the variables most often evaluated were time on dialysis, diabetic status and transplant history. Although the complex nature of phosphate binder regimes was not widely evaluated in the literature, it was reported to have a significant role in binder adherence. This relationship has already been discussed in this chapter (Tomasello et al., 2004).

Finally, Karamanidou et al (2008) also identified the psychosocial variables, including health beliefs, personality, health locus of control, social support, family dynamics, anxiety / depression and copying style, as being least evaluated for potential associations with adherence to phosphate binders. It has been suggested that these psychosocial variables may be more closely associated with adherence than the demographic and clinical variables which are more commonly analysed.

The results obtained in this study appear to support results previously reported that patients tend to self-report good adherence to their phosphate binder medication. In clinical practice this situation may cause a problem for renal doctors, dietitians and pharmacists, during a consultation, when it is obvious from the patients' blood results that they are not routinely taking their prescribed dose(s) of medications.

Patients' contact time with pharmacists and dietitians

No additional medical staff time was required with the PMP group. In contrast, the renal pharmacist, who did not routinely conduct monthly blood and drug reviews for HD out-patients, spent on average 19 [8 - 25] minutes per month with PMP group patients, for the duration of this study.

The amount of time that pharmacists spend on different patient related activties, including counselling, has been published (Oh et al., 2002). This article was written in relation to health care insurance payments for pharmacy services in North America. Payments made to dispensing pharmacies are commonly based on the cost of the medication in addition to a standard dispensing fee to cover routine pharmacy services. Historically, North American pharmacists have refrained from offering more detailed advice or counselling to patients due to this payment scheme. However it has been acknowledged that pharmacists are well placed to extend their role to provide medication reviews and intensive counselling with the aim of improving patients' knowledge regarding the medicines they should be taking and thereby reducing poor adherence. The situation described by Oh et al (2002) is comparable to the role the renal research pharmacists undertook in this study, therefore the

time requirements allocated to specific activities were of interest and are summarised in Table 5.2. As a guide, using the average time spent for relevant activities in each category the estimated time required by the renal pharmacist, during the current study, would be approximately 27 minutes. This is comparable to 19 [8 - 25] minutes per month the renal pharmacists spent with PMP group patients only. The authors advised that this data should be used with caution as it may not be appropriate to use these time requirements for pharmacists working with chronically ill patients. Haemodialysis patients would fall into this category of patients therefore factors related to counselling patients would need to be taken into consideration for example, multiple medications per patient, posible poor drug adherence, literacy level and cognitive impairment. The authors recommended that additional data must be collected including patient demographics and accurate time and motion studies of pharmacists working with various patient populations.

The renal dietitian also spent additional time discussing the patients' blood results and formulating treatment plans with the renal pharmacist, whereas monthly dietetic reviews, for patients at each HD site, was routine clinical practice. Unfortunately, in this current study, the renal research dietitian did not collect time and motion data to quantify the additional time spent on patient related activities. Dolecek et al (1995) published results regarding the time spent by renal dietitians as part of the Modification of Diet in Renal disease (MDRD) study. In the discussion the authors quoted data which associated 30 minutes of nutritional counselling per HD patient weekly, by a renal dietitian, with potentially reduced hospital admission rates. Another survey reported that renal dietitians spent on average 1.7 hours per patient monthly, Interestingly, on average the consultant spent 0.73hrs with each HD patient every month (Dolecek et al., 1995). These surveys were all conducted in North America where dialysis services are able to provide a better staff to patient ratio which enables staff to dedicate more time on routine counselling sessions with their patients.

At BLT, due to the large HD patient population and small renal dietetic workforce, dedicating two hours of dietetic time per patient monthly would not be feasible. An approximate time spent by the renal dietitians on a phosphate management review, during the current study, would have been 20–30 minutes compared to 10-15 minutes for PMP and SP groups respectively. Therefore, the research dietitian was able to dedicate double the amount of time with patients. It must be acknowledged that patients who are persistently poor at adhering to diet and drug treatments require additional counselling

which means this additional time will need to be incorporated into routine clinical practice by renal pharmacists and renal dietitians.

In summary, extending clinical practice roles of the renal pharmacist and renal dietitian may have implications to future renal work-force planning, staff costs and time management.

Table 5.2

Summary of mean time requirements for pharmacists undertaking various patient-related activities (Oh et al., 2002).

Item	**Time (minutes) Mean±SD**
Appropriateness of therapy	
• Drug or indication	4.9±5.2
• Dosage regimen or strength	4.9±5.4
• Dosage form or route	5.1±5.9
• Quantity or duration	4.7±4.9
Monitoring	
• Adverse effects or toxicity	5.4±5.1
• Duplicate therapy	2.9±2.7
• Noncompliance	3.7±3.6
Interaction	
• Drug-drug	4.2±4.3
• Drug-disease	6.5±5.2
• Allergy or sensitivity	4.7±4.8
Action	
• Patient contacted	3.2±2.9
- Counselled about problem	3.5±3.3
- Information from patient resolved problem	2.9±2.4
• Referral	
- To prescribing physician or other provider	7.3±6.2
- To another allied health care professional	2.7±1.3
Disposition	
• Prescription dispensed as written	3.5±3.5
• Prescription changed and drug dispensed	5.1±5.3
• Drug not dispensed	6.4±7.0

5.1.3 Revised phosphate knowledge questionnaire

Questionnaire content validity

During the development of the revised questionnaire the content validity was reviewed by the renal healthcare professionals in the renal research team. This team discussed and agreed the topics that were included in the final questionnaire. In contrast to this study, Schlatter et al (1998) stated that the phosphate knowledge assessment tool used in their study was checked by three experienced renal nurses for its content validity. The availability of phosphate questionnaires used in previously published studies also helped to confirm the content validity of the questionnaire used in this study (Stamatakis et al., 1997, Poduval et al., 2003). Therefore, it can be stated that the researchers were confident that the questionnaire included in this current study was appropriate to evaluate HD patients' phosphate knowledge. The information discussed in this section is able to demonstrate that content validity, can be assessed qualitatively.

In contrast, all of the other reliability and validity variables which should be included in the development and evaluation of questionnaires are statistically measurable and there are also standard cut-off values beyond which items or scales become unacceptable (Parmenter et al 1999). Testing reliabilty or confirming a questionnaire's reliability should always be paramount before it is used as an assessment tool in research or in clinical practice. In the following section various methods wll be discussed that have been described in the literature.

Questionnaire reliability

The purpose of the test-retest using the same individuals was to determine the reliability of the phosphate questionnaire. The aim of this test is to confirm that the results obtained were consistent. Questionnaire reliability testing, in this current study, was assessed using five haemodialysis patients who did not participate in the main study. The first and second interviews were face-to-face and telephone call respectively. The researchers did inform the patients what they were being asked to do before they agreed to participate . Once the patients knew the topic under interest they were able to improve their knowledge before the re-test, a week later. This may explain why one subject achieved a higher score when retested i.e. three points more than on the initial testing. It is feasible that this patient referred to information, previously received, prior to the re-test to ensure a higher score was achieved. The gap of one week cannot be explained by a specific rationale instead it may have been chosen arbitrarily. A Bland and Altman plot was produced using paired

measurements for each patient surveyed (Figure 4.5). Since the differences in the paired measurements fell near to the zero line, there was little difference between the results obtained and therefore they were deemed reliable.

A comparison between the method used for testing reliability in this current study and other studies using questionnaires was undertaken. Parmenter et al (1999), undertook test – retest reliability for a nutrition knowledge questionnaire using 105 subjects. They used a two week interval between the two tests and stated the rationale for this time interval was that this was sufficient time for the subjects not to remember their original answers or for them to change their knowledge on the particular topic being tested. To ensure the latter was unlikely to occur the researchers did not inform the subjects that they would be asked to complete the questionnaire again. The results were statistically analysed using Pearson's correlation to assess the difference between the scores. The reliability was 0.98, recommended minimum value is 0.7, thereby demonstrating that a sample size of 100 subjects provided strong correlation.

Prowant et al (1989) also designed and piloted their questionnaire before using it for the main study. Despite acknowledging amendments were made, after the pilot, reliability of the questionnaire was not reported. In contrast, Stamatakis et al (1997) described the use of a reliability coefficient kappa to measure the difference between the paired measurements, with a two month interval between tests. They concluded that a moderate consistency in the responses was achieved between the first and second test. Two other studies, using questionnaires did not report reliability studies (Schlatter et al., 1998, Poduval et al., 2003).

It must be acknowledged that the methodology for testing the reliability of the phosphate knowledge questionnaire, used in the current study, was not as robust as it should have been. Instead of using a sample of approximately 100 subjects only five patients were tested and therefore statistical analysis was not feasible.

Patients' opinions of current phosphate management practices

The issues discussed in this section of the questionnaire were included to ascertain patients' opinions of current practices in the unit where they dialysed. All study patients were asked if they were informed by the HD unit staff about their serum phosphate level each month (Figure 4.6). Only 28% of the PMP group patients answered yes to this question, at the end of the study, compared to 53% of the SP patients. This result was not expected, in view of the fact that part of the intervention was to individually counsel the

patients, face-to-face, whilst they received their haemodialysis and discussing phosphate levels would have been part of this. The patients may not have remembered the details of conversations during dialysis and, if so, this suggests that this time is not optimum for education or advice giving.

Patients were also surveyed on whether they asked HD staff what their serum phosphate level was each month (Figure 4.7). Post intervention, 7% fewer PMP patients asked the staff compared to a 9% increase in the SP group. This result may be demonstrating the difference in staff input between the two study groups.

Earlier in this chapter evidence to support the differences between the study groups relating to patient contact with renal staff was discussed. Although the SP group patients were participating in a phosphate study they appeared to receive less attention than patients in the PMP group for the duration of the study. Therefore it is possible that the SP group patients became more interested in their monthly serum phosphate levels and this may have resulted in them being more inclined to ask the HD staff. Finally, these questions were included as part of the questionnaire to ascertain patients' opinions of current practices in the unit where they dialysed. Since these questions were not deemed as having a right or wrong answer they were, therefore, not included in the total knowledge score.

Phosphate knowledge of haemodialysis patients

i) Total score

The results for the total knowledge scores showed that the intervention did not achieve a significant increase in patients' phosphate knowledge. This finding may suggest that the content of the conversations which occurred, between the individual patients in the PMP group and the renal research pharmacist and renal dietitian, may have been more focussed on specific instructions on necessary medication and diet changes rather than more general phosphate education. Conversely, the study results also indicated that 50% of the potential correct answers were not achieved by patients in both study groups. A detailed evaluation of the correct answers obtained to individual questions has identified topics, relating to hyperphosphataemia and its management, where patients' knowledge was inadequate.

It must be noted that, a negligible reduction in phosphate knowledge scores was observed, in both the study groups, post intervention. This is surprising as it was not anticipated that patients would know less as their education was ongoing. This result was not expected, in view of the fact that part of the intervention was to individually counsel the patients, face-to-face, whilst they received their haemodialysis. It is unfortunate to have to report these

disappointing results in relation to, what would appear to be, ineffective patient education. However, possible explanations include random error, bearing in mind that, the development and evaluation of the questionnaire did not achieve "gold standard" methodology.

The patients may not have remembered the details of conversations during dialysis and, if so, this suggests that this time is not optimum for education or advice giving. For an individual to retain information being mentally alert is paramount. It has been documented in the literature that dialysis patients suffer cognitive impairment (Madan et al 2007, Murray et al 2007). Madan et al (2007) recruited 15 HD patients, assessed changes in cortical brain function, to determine whether the changes could be attributed to haemodialysis directly. Measurements were taken two hours before and two hours after HD. Results were compared to age and sex matched controls. The main finding was that after HD the cortical function of the HD patients had decreased and the readings were comparable to the control group. The researchers concluded that the removal of ureamic waste products, by HD, resulted in improved cognitive function. Based on this result it suggests that it may be beneficial to test HD patients' knowledge post dialysis. However, it would have been useful for this study to have incorporated a mental test pre and post HD to verify that an improvement in cognitive function had occurred.

Murray et al (2007) reported that HD patients' cognitive function was at its best a day after HD. They conducted a study, on 28 HD patients, to determine the cognitive function at four different time-points which included 1 hour into HD session. They found the worst results were obtained during HD and the best results were either 1 hour before HD or the next day. Consequently, they concluded that clinicians may prefer to choose appropriate times to see patients when they may be more alert, more responsive and therefore more able to retain the verbal information told to them. In reality, these results will pose problems for clinical staff as HD patients tend not to want to be delayed starting their HD session and the following day they are at home.

A few authors have stated, as part of the inclusion criteria for recruitment, that patients must be mentally alert. Schlatter et al (1998) reported the mental state of patients was based on the subjective judgement of the head nurse. Whereas Ford at al (2004) referred to patients being mentally competent to answer questions. The latter was also the case in this current study. However, in hindsight, it would have been useful to assess cognitive function objectively, as it is a potential confounding factor closely associated to change in HD patients' phosphate knowledge scores.

Ford et al (2004) carried out a randomised controlled trial whereby half of the HD patients received a thirty minute education session, from a dietitian, for six consecutive months. Phosphate knowledge was tested both pre and post intervention. The phosphate knowledge questionnaire, used in this study, was developed and pilotted by the researchers. The final questionnaire had a MCQ format, comprised of twenty questions and, due to the low literacy of the study patients, was administered by interview with the researcher recording the answers. The patients who received the additional education sessions demonstrated a significant increase in knowledge score, post intervention. The change in the mean score, for the intervention group, was 9% ($P < 0.05$) compared to 2% increase in the control group (P = ns). These results provide evidence that a focussed education intervention, specially tailored for the patients' intellectual level, can be effective.

Poduval et al (2003) described how their original questionnaire was rated against two North American validated readability scores. This enabled them to compare the questionnaire to school reading levels.

It must be stated that written information was incorporated into the phosphate knowledge education. For example patients were given low phosphate diet information and a peronalised medication card. In view of the issues surrounding patients' cognitive function, at the time counselling was undertaken, it would seem that the provision of suitable written resources was very beneficial as it allowed patients to take it home with them. They would then have information to read and refer to when they are at their most alert and also show it to their family and carers which would help foster the social support which has already been identified as relevant to patient adherence. Ford et al., 2004 actively encouraged their study patients to keep the resources provided safely in a file at home.
With respect to tailoring the phosphate knowledge questionnaire and education resources to patients' education level this was not undertaken in detail as part of design process of this current study. However, the researchers, who have had previous experience writing patient information leaflets, which must be BLT validated and approved before they can be used with patients, did aim to apply these skills during this task.

ii) A summary of the phosphate knowledge results

Evaluating the breakdown of correct answers obtained from study patients yielded some interesting results. More PMP group patients knew the target blood phosphate level compared to patients in the SP group (Table 4.7). Awareness of optimum serum phosphate

levels were allocated a total score of two points, which patients' obtained if they were able to state the correct lower and upper levels for target range. At the time the proposal was written, target serum phosphate levels were based on The Renal Association guidelines (2002), hence the range 0.8 – 1.8mmol/l was deemed as correct answers. However, the subsequently published National Kidney Foundation (2004) targets, 1.13 - 1.78mmol/l, were used in the results to enable comparisons with other studies to be undertaken. A trend demonstrating an improvement in patients' knowledge was observed post intervention but this was not a significant increase in either study group (Table 4.7).

A possible reason to explain why a high percentage of the study patients, were able to state that itchy skin was a symptom of high serum phosphate levels was perhaps because they had personal experience of this common symptom, alternatively they may have overheard conversations, whilst dialysing, between other HD patients and clinical staff.
In contrast fewer study patients, in both groups, knew that red eyes were a symptom of hyperphosphataemia (Table 4.7). This may indicate that, in contrast to itchy skin, red eyes is a symptom which patients experience less often. Also renal staff may not have informed patients that this is symptom they may experience.

Apart from the effect elevated serum phosphate levels may have on bones, patients did not appear to know the other parts of the body that could be affected, which were mainly related to soft tissue calcification. The fact that the majority of patients' knew the association between hyperphosphataemia and the effect on bones could possibly be due to the fact that bones are also affected by secondary hyperparathyroidism and patients may relate this explanation to bone pains they may have personally experienced. It is also possible that renal unit staff previously have focussed on bones being the main side effect of hyperphosphataemia and only more recently, with the evidence that has emerged regarding soft tissue calcification are now beginning to incorporate include these complications when educating patients. However, patients may tend to acknowledge and remember early symptoms that they may have experienced rather than longer term symptoms which they may not think as been as serious but are actually life threatening.

The other effects of persistent hyperphosphataemia were less well known (Table 4.8). These results may demonstrate that, at the time of this study, patient education regarding hyperphosphataemia appeared to have focussed on the effect it has on bones. This study may have identified a possible gap in patient education, especially in relation to

calcification of soft tissues, for example the heart and blood vessels. These results support the findings reported by Durose et al (2004) regarding patients' lack of knowledge specifically in relation to medical complications.

Finally, evaluating patients' knowledge of phosphate management highlighted that patients appeared to know that phosphate binders and a low phosphate diet were both treatments to correct hyperphosphataemia (Table 4.6). Whereas patients' awareness that haemodialysis also has a role in lowering serum phosphate levels was less well known (Table 4.7). These results are understandable since patients are routinely counselled regarding their diet and phosphate binders whereas the functions of the HD machine may be explained in general rather than specific terms. Interestingly, the SP group were less knowledgeable on this particular matter which is difficult to explain, especially for the pre-intervention results, as the patients were randomly assigned to a study group.

iii) Dietary phosphate knowledge

The revised questionnaire, used in the main study, aimed to determine whether the study patients knew which foods rich in phosphate they needed to avoid completely compared to those that could be included in the diet, in limited quantities. These results have demonstrated that HD patients, who participated in this study, appeared to have a reasonably good knowledge regarding their low phosphate diet prior to commencing the study. The level of knowledge was maintained at the end of the study. Reductions in the percentage of correct answers obtained was observed, in a few cases.

Durose et al (2004) conducted a study to determine HD patients' knowledge regarding their renal diet and medical complications of hyperphosphataemia. A questionnaire was designed and initially piloted on ten patients before being used in the main study. The mean serum phosphate level, of the patients who participated, was 1.9±0.5mmol/l. Thirty-one percent of these patients had a serum phosphate level greater than 2.0 mmol/l, which is comparable to the prevalence data discussed in chapter 1.

In this study Durose et al (2004), stratified the knowledge scores into two categories according to a percentage of the total score achievable. A low and a good score were defined as 0 - 50% and 51 – 100% respectively. Patients' knowledge was found to be poor, for medical complications, with a mean score of 29% compared to a good score of 53% for dietary knowledge. It must be noted that these researchers tested patients' on all aspects

of the renal diet and found that their dietary phosphate knowledge yielded the lowest scores.

The phosphate knowledge results obtained in the current study appear to agree with results, reported by Durose et al (2004), regarding HD patients' lack of knowledge relating to medical complications associated with hyperphosphataemia. Identifying these topics was a useful exercise as it has highlighted areas that need addressing for future patient education sessions and resources.

5.2 Relationships Between Variables

5.2.1 Single variable linear regression

Single regression analysis aims to predict an outcome for a dependent variable from a single independent variable whereas multiple regression analysis aims to predict a outcome for a dependent variable from several independent variables (Field 2005).

This regression analysis did not show a significant relationship between the change in serum phosphate level (dependent variable) and change in phosphate knowledge score (independent variable), for either study groups. However, a significant relationship was found between change in serum phosphate level and another independent variable, study group ($P = 0.03$) (Table 4.11). The change in serum phosphate level was also predicted by the single variable analysis equation, shown in the section 4.9 of the previous results chapter. These results indicate that if a HD patient was managed by experienced renal health care professionals, using a phosphate management protocol, a small reduction in the serum phosphate level would be expected, within a four month treatment period. In contrast, a HD patient receiving standard practice would be expected to have a small increase in their serum phosphate level, within the same time period. The single regression analysis predicted a reduction in serum phosphate level for the PMP study group only (see regression equation section 4.9). Therefore this result could be used as evidence to support the use of a phosphate management protocol over standard treatment, due to the fact that 17 patients per study group was deemed to be a sufficient sample size based on a retrospective power calculation that a minimum of 15 patients per group were required for this current study.

To date, the results of studies to investigate the relationship between serum phosphate levels and phosphate knowledge in HD patients remain inconclusive. This may be due to

the fact that serum phosphate levels were often used as the measure of poor adherence to phosphate treatments. However, the routine use of serum phosphate levels, as the main outcome measure, in many studies has been questioned in a recent systematic review article which evaluated phosphate binder precription adherence in haemodialysis patients (Karamanidou et al 2008). The authors explained that serum phosphate levels can change as a result of various confounding factors including residual renal function, nutritional status, type and adequacy of dialysis.

Stamatakis et al (1997) reported a significant correlation between lower serum phosphate levels and good phosphate knowledge scores (P = 0.028). Whereas Poduval et al (2003) observed a high prevalence of poor knowledge regarding both dietary phosphate and medical complications associated with elevated CaxP product levels. These studies were discussed in detail in chapter 1.

Ford et al (2004) achieved significant improvements in both serum phosphate levels and phosphate knowledge, for patients who received six consecutive months of education. These results have been discussed earlier in this chapter. It must be noted that the control group also improved, but insignificant results for both serum phosphate levels and phosphate knowledge, at the end of the study. A possible explanation, suggested by the researchers, was that the additional attention these patients received from being study participants may have resulted in the positive effects observed. This is described as the "Hawthorne effect" (McCarney et al., 2007). These studies appear to support the assumption that patients who have better phosphate knowledge are able to achieve lower serum phosphate levels.

Durose et al (2004), obtained mixed results when comparing knowledge and serum phosphate levels. Firstly, patients with normal range serum phosphate levels had the lower knowledge scores regarding medical complications (P = 0.002). This result suggests that patients achieved target or normal range serum phosphate levels without knowing the complications associated with hyperphosphatatemia. Secondly, patients with higher knowledge scores regarding medical complications also achieved higher dietary phosphate knowledge scores (P = 0.003). This result demonstated that haemodialysis patients can achieve good knowledge on different topics related to phosphate management. Finally, the patients who achieved higher dietary phosphate knowledge scores experienced more difficulty adhering to dietary phosphate restrictions (P = 0.03). The study authors

explained this result in relation to HD patients having a higher protein requirement. Since many foods rich in protein are also rich in phosphate, these patients may have chosen phosphate rich foods in an attempt to adhere to consuming an adequate amount of protein. The close relationship between protein and phosphate in food has already been discussed in chapter 1.

The results of this current study were unable to provide evidence to fully support or contradict the findings from other studies. However, this study was able to demonstrate, for the PMP study group, a small reduction in the mean serum phosphate level after intervention without any improvement in phosphate knowledge score. Thereby suggesting that it is possible to improve the serum phosphate levels in HD patients without a corresponding increase in phosphate knowledge. It must be mentioned that HD adequacy was the only confounding factor of which data was collected and analysed in this current study. Relevant data that was not collected as part of this study will be discussed in more detail later in this chapter.

5.2.2 Evaluating the contribution of individual independent variables

It must be noted that in the present study only 26% of the variation in the change in serum phosphate level was attributed to the five independent variables used in this linear regression analysis, which included study group, change in phosphate knowledge score, age, time on HD and gender. This indicates that the remaining 74% of the variation of the change in serum phosphate level, was associated with other variables that were not included in the regression analysis. It is possible that variables pertaining to phosphate binder adherence, discussed earlier in this chapter, may also be relevant in predicting change in serum phosphate levels. These independent variables were grouped into three categories which were demographic, clinical and psychosocial. The variables in each category that were not included in this regression analysis are summarised in Table 5.3.

Poduval et al (2003) identified level of college education as a demographic variable significantly associated with CaxP product level and found that HD patients with lower levels of education had elevated CaxP product levels ($P = 0.04$). This study has already been discussed in detail in chapter 1. In this current study information on the level of education achieved by the study patients was not collected.

It would appear that this current study has copied previous studies by collecting the standard demographic and clinical data and omitting potential relevant psychosocial data.

Consequently, this study has been unable to identify additional independent variables which may contribute to the variation in the change in serum phosphate levels.

Table 5.3

A summary of potential independent variables for predicting a change in serum phosphate level (Karamanidou et al., 2008)

Predictor Category	List of potential independent variables
Demographic	Level of education, marital status, income, employment status, religion
Clinical	Aetiology of chronic kidney disease, diabetic status, transplant history, regimen complexity
Psychosocial	Health beliefs, personality, health locus of control, social support, family dynamics, anxiety / depression, coping style

5.3 Limitations of the Study

5.3.1 Study population

Sample size

The retrospective power calculation, stated statistically significant results could be achieved by having a minimum of 15 patients in each study group whereas 17 patients per group was actually achieved. Therefore, despite the sample size appearing to be small it actually was sufficient for detecting a significant change in the primary outcome measure, which, in this instance, was a change in serum phosphate levels. However, this may not be the case for detecting a significant change in a secondary outcome measure such as phosphate knowledge scores.

Racial groups

Another area to address is the fact that BLT patient population is racially diverse and, therefore, some patients were excluded due to the language barrier. In this study it was necessary to exclude non-English speakers as to include them would have required the use of translators, which meant the introduction of an unquantifiable confounding variable.

Relying on professional interpreters, who may not have dietetic, pharmaceutical or medical training, to participate in patient education sessions, is a concern. These studies also raise issues regarding the potential cost implications.

5.3.2 Phosphate management protocol

Blood sampling and analysis

Although a statistically significant difference in the change of serum phosphate levels has been observed between the two groups, this small change is unlikely to have clinical significance. The time period for evaluating the full effectiveness of the PMP intervention was insufficient, based on the negligible change in iPTH levels after a 4 month period, this would appear to be the case for this serum variable.

The study conducted by Moe et al (2005) which has already been discussed earlier in this chapter, in relation to standard drug treatment (control group) and its effect on iPTH levels had a study duration period of 26 weeks (6 months). Other serum biochemistry levels measured included seum phosphate and CaxP product. The baseline and end of study median (interquartile range) serum phosphate levels for the control group were 2.0 (1.65, 2.3) mmol/l and 1.91 (1.65, 2.16) mmol/l respectively. Baseline and end of study serum CaxP levels were 4.92 (4.14, 5.71) pmol/l and 4.74 (4.14, 5.41)pmol/l respectively. The change in serum iPTH levels was +4pmol/l by the end of the six months, which suggests that, due to the persistently elevated serum phosphate levels, increasing the doses of alfacalcidol by a generous amount was not feasible for many of the patients.

These results indicate that six months was also insufficient time to achieve average values for relevant serum parameters within the K/DOQI targets, when using traditional treatments for SHPT. Also, it would appear that, in this current study, PMP intervention in conjunction with phosphate binders and alfacalcidol did achieve slightly better results in a shorter time period of 4 months. Overall, based on the results of the two studies, choosing an intervention period of six months or less would appear to be too short a timescale to observe significant changes in serum biochemistry when the aim of the study is to evaluate the effectiveness of a phosphate management tool.

Nutritional variables

No dietary data were collected during this study so the adequacy of patients' nutritional intake and any significant changes in dietary phosphate intake post intervention is unknown.

Accuracy of BMI data may be questioned since patients' were not assessed to determine whether they were retaining fluid post dialysis. Also high blood pressure, another indication of fluid retention, was not recorded either. It must be mentioned that neither the renal dietitian or renal pharmacist is trained to conduct physical assessments of HD patients to determine their fluid status. However recording and identifying patients with high or low blood pressure would have been feasible.

5.3.3 Revised phosphate knowledge questionnaire

Phosphate binders

In the phosphate knowledge questionnaire, the evaluation of the types of phosphate binders taken highlighted that a small number of patients were taking calcium acetate and sevelemer hydrochloride, which are to be taken with food. Therefore, only marking 10 minutes or less as the only correct answer was an error. Also the accuracy of self reported adherence may have to be questioned as a time period, for example in the last four weeks, should have been included in the question, to help patients' clarify their level of adherence.

Patients' opinions of current phosphate management practices

The accuracy of patients' opinions of current phosphate management practices may also have to be questioned since a time period should have been included in these questions. Therefore, if it was stated that the response required referred to the last four weeks this would have helped patients' clarify their answers to these questions.

Phosphate knowledge of haemodialysis patients

Although the main racial group in our study population was white, other racial groups were represented (Table 4.1). In contrast the food items used as examples in the questionnaire were of western origin. This may have resulted in some patients scoring lower marks for phosphate knowledge, due to their lack of knowledge of foods they did not usually consume.

5.3.4 Relationships Between Variables

Single variable linear regression

From the results of the regression analysis undertaken during this study, it has become apparent that there were other variables that should have been included, which were not, in the patient data collection. These contribute to the 74% of the variation in serum phosphate levels which was not accounted for. The variables might include aetiology of

kidney disease, education level, marital status, dietary phosphate intake, phosphate binder type / dose and health beliefs. These are just a few examples, however a more detailed list can be found in Table 5.3.

5.4 Review of the study hypotheses

The hypotheses of this study were two-fold. Firstly, a PMP used by renal pharmacists and renal dietitians can help HD patients with hyperphosphataemia achieve target serum phosphate levels (1.13 – 1.8mmol/l). This study appears to have provided tentative support to this hypothesis. However, it has to be acknowledged that the mean serum phosphate level achieved, within the four month intervention period, was upper end of the target range. Therefore some of the patients in the PMP group had serum phosphate levels above the target range at the end of the study. Also, the mean change in serum phosphate level between the study groups achieved statistical significance due to the increase in serum phosphate levels, in the SP group, post intervention.

The second hypothesis was that there would be a significant relationship between the change in serum phosphate levels and the change in patients' phosphate knowledge scores after a phosphate management protocol was used to improve serum phosphate levels in haemodialysis patients over a 4 month study period. Unfortunately, a significant change in phosphate knowledge score was not achieved post intervention in this current study. Consequently, the regression analysis was unable to demonstrate a significant association between change in serum phosphate level and a change in phosphate knowledge score. Therefore, this study has not been able to provide additional information to clarify the relationship between serum phosphate levels and phosphate knowledge scores.

5.5 Potential for future studies

5.5.1 Study population

Sample size

A recurrent problem experienced by researchers is the inability to recruit the target number of patients required to ensure data can be statistically analysed. One possible solution is for more researchers to collaborate in multi-centre studies. Novice researchers may not feel confident to attempt ambitious research, whereas experienced researchers may be willing to consider this as a feasible option. The way forward may be the development of research teams which consists of members with mixed research experience and abilities. The inexperienced researchers would benefit from support provided by more experienced

researchers, whilst undertaking their smaller research projects. The overall outcome should be good quality research studies, using standardised methodological techniques and robust statistical tests for data analysis.

Also a study, with a larger sample size, is required to determine whether the effects observed in this study can be extended to both national and international haemodialysis patient populations.

Racial groups

Patients who do not speak English require equality in the treatment they receive and they should be included in future research studies. However, in routine clinical practice, patients who do not speak English, are more likely to be at a disadvantage where information and advice regarding their treatment and well-being is concerned. As previously discussed, during the current study, the time that the renal dietitians and pharmacists had available to spend with each study patient was limited when compared to data from North America.

The involvement of an interpreter, for non-English speakers, is normally associated with a longer patient consultation. Alternatively, if an interpreter is not available, then the healthcare professional would have to resort to a telephone conversation with a relative or carer and supporting written information is given to the patient for their relative / carer to read and explain to them in their home environment.

Therefore, in terms of developing a research project, involving non-English speakers, the issues mentioned here will need to be taken into consideration. Pilot studies should be undertaken to ascertain the cost of using both interpreters and translators and the impact of their involvement with regards to communicating with study patients.

5.5.2 Phosphate management protocol

Blood sampling and analysis

To determine whether the phosphate management protocol could produce a change in serum phosphate levels which has more clinical significance, the study could be repeated but this time recruiting patients with more poorly controlled serum phosphate rather than a population with a single serum phosphate level above 1.8mmol/l. A longer intervention, greater than six months, and follow-up period would also allow for potential significant changes in serum phosphate, CaxP product and iPTH levels to be observed. To prevent patients having to withdraw due to severe secondary hyperparathyroidism it may be

beneficial for an upper limit for serum iPTH levels to be incorporated into the inclusion criteria in future studies, for example 85pmol/l.

Urine sampling

It would be beneficial to measure the residual renal function of patients or record whether they were anuric, which was not done in the present study. This will help to determine whether there is a relationship between HD patients' who continue to pass some urine and lower serum phosphate levels. Residual renal function has been named as a potential confounding variable for change in serum phosphate level (Karamanidou et al., 2008).

Nutritional variables

In future studies, the additional measurement of nutrient intake would allow the effect of dietary advice on phosphate intake to be directly evaluated as well as facilitating the examination of overall nutrient intake adequacy. However, the time required to undertake this additional data collection to a high standard would add considerable cost to the study. Also additional data to ensure haemodialysis patients are achieving their desired dry weight should be included in future studies. Thorough data collection will demonstrate to fellow renal professionals that the study aimed to achieve the highest level of accuracy. This suggestion has also highlighted the potential for renal dietitians to be taught physical assessments skills to ensure patients' dry weight is regularly monitored and any discrepancies are dealt with promptly (Daugirdas 2001).

Phosphate Binders

A large prospective study will be required to determine whether utilising a combination of phosphate binders might be an effective way to reduce the long term risks associated with individual binders. Future studies assessing patients' adherence to their phosphate binder regime, with respect to timings of doses and meal-times, will need to take into account the different instructions patients are given depending on the type of phosphate binder they have been prescribed.

Phosphate management protocol and patient education from dietitians and pharmacists

Based on the cognitive function results reported in the literature, some of which has been discussed earlier in this chapter, it will be necessary to educate HD patients' and then assess their knowledge, at the most appropriate time, to hopefully produce the most positive results in future studies. It has been suggested that before patients have HD and

non-HD days are the times when patients may be more receptive to learn new information (Madan et al., 2007, Murray et al., 2007). However researchers may find it problematic recruiting patients if the study involves additional hospital visits. Alternatively, researchers could try to limit the time period for advising patients to the first two hours of their dialysis, when they are least likely to start experiencing any adverse side effects of the HD, for example nausea and low blood pressure. It would also be useful to collate cognitive function data on the HD patients, who participate in education intervention studies, in the future.

Future studies are also needed to evaluate the health economic implications of the phosphate management protocol with regard to both staff time and prescribing costs in view of the potential clinical benefit.

This study may have identified a possible gap in patient education, especially in relation to calcification of soft tissues, for example the heart, skin and blood vessels, thereby including calciphylaxis. The gaps identified in patient education should also be further explored in the HD patient population.

Assessing haemodialysis patients' willingness to learn and motivation to change

To investigate these issues may require collaborations with clinical psychologists. For example developing and piloting an adherence assessment tool incorporating demographic, clinical and psychosocial factors, to use on both new and established haemodialysis patients would be very useful in routine clinical practice.

Developing new education strategies

At present all haemodialysis patients tend to receive low phosphate diet and phosphate binder education in the same format, but the members of staff, providing the advice to patients may be different. In view of the points raised in the literature which highlight that haemodialysis patient populations are a heterogenous rather than a homogeneous group of individuals, it may be better to tailor an educational approach to an individual's learning style (Morton De Souza (2004, 2006). Three learning style categories have been described which are visual learners, auditory learners and tactile learners (Morton De Souza 2006).

Renal health care professionals, especially dietitians, need to develop and utilise a variety of educational resources. It will be necessary to evaluate the effectiveness of these resources before they can be incorporated into standard practice. Therefore, this could lead

to many research projects opportunities in the future. The widespread use of resources, already in existence, that have been proved effective through scientific evaluation should also be encouraged (Ashurst et al., 2003, Ford et al., 2004). Ashurst et al (2003) used patient education resources produced by Genzyme Inc, the pharmaceutical company who produces the phosphate binder Sevelamer. Ford et al (2004) used education resources tailored to the low literacy levels of their study patients. This was demonstrated by the description of flipcharts, puzzles, clourful, eye-catching small chairside posters and picture handouts. These were produced by an American Renal Dietitians Practice Group and resulted in positive patient feedback.

Morton De Souza (2004) provides a basic list of imaginative ways to help educate HD patients, which also takes into account patients' literacy skills and limited staff time. Since the HD population at BLT, is multi-racial and may also include some patients with disabilities, the phosphate education resources need to be appropriate to all of the patients under the renal unit's care. In this technological age there are many electronic audio-visual aids available which could help staff educate patients and at the same time reduce the face-to-face contact time staff need to spend with individual patients. The use of interactive DVDs could help engage younger HD patients, identified as a group more likely to have problems adhering to treatment regimes. However, it is important not to assume that technology will just benefit the younger patients. Some older patients are also comfortable using modern technology.

5.6 Contribution to the Body of Knowledge

This study addressed the issue of achieving improved serum phosphate levels in HD patients with hyperphosphataemia by extending the roles of renal dietitians and renal pharmacists through using a phosphate management protocol. This study was able to demonstrate that HD patients were able to achieve a reduction in the mean serum phosphate level, whilst managed with a protocol when compared to HD patients receiving standard management. At the end of the study, trends towards other positive outcomes were also observed in the PMP group, for example the beginning of a reduction in median iPTH levels and achieving multiple K/DOQI serum targets. The protocol document contained safety aspects including guidelines on maximum doses for the phosphate binders and vitamin D analogue. It also clearly stipulated when the researchers should refer patients to the consultant. Therefore, the relevance of this PMP is that it was used safely by

experienced renal healthcare staff, who were not doctors, thereby making it potentially an exciting clinical practice development. As already stated, studies with larger numbers of patients need to be undertaken to confirm whether these observed effects can be extended to other haemodialysis populations, but the present results provide evidence that a phosphate management protocol can achieve better results than less coordinated standard practice routines. By publishing this current study, in a recent article, relevant information has been disseminated in this area of clinical research (Yokum et al., 2008). This addition to the body of knowledge, will hopefully, contribute to the impact protocols will have on future phosphate management in the HD patient population.

5.7 Conclusion

The aims of the current research undertaken was firstly, to evaluate the effectiveness of a new phosphate management protocol designed to achieve serum phosphate levels set by the National Kidney Foundation (2004) for patients undergoing regular haemodialysis. The hypothesis tested by this approach was that renal pharmacists and renal dietitians can help HD patients with hyperphosphataemia achieve target serum phosphate levels (1.13 – 1.8mmol/l), by following a defined PMP, for 4 months. This current study demonstrated that HD patients were able to achieve significantly better control of serum phosphate levels whilst managed with a protocol when compared to HD patients receiving standard management.

The second aim was to evaluate patients' phosphate knowledge, pre- and post-intervention, regarding medical complications associated with hyperphosphataemia and treatments for managing serum phosphate levels. The hypothesis tested was that a significant relationship existed between the change in patients' phosphate knowledge scores and the change in serum phosphate levels after the protocol was used to manage serum phosphate levels in the same haemodialysis study patients for 4 months. A significant relationship between a change in serum phosphate level and change in phosphate knowledge score was not observed.

The results of this study have firstly, provided some evidence to support further investigation of the use of a PMP in clinical practice is warranted. Secondly, the results have highlighted the need for a thorough review of patient education regarding phosphate management, including the renal staff involved, types of resources used and the most effective time to deliver the information to patients.

In summary, this study indicates that a phosphate management protocol could potentially be added to the clinical practice strategies to help achieve the long-term goal of a significant reduction in the prevalence of hyperphosphataemia and its associated complications, although a larger study is required to confirm its true effectiveness. Although improving phosphate knowledge of HD patients especially regarding the medical complications of hyperphosphataemia would seem, in theory, to be beneficial no relationship was observed between changes in patients' phosphate knowledge and changes in serum phosphate levels. This may reflect the small group of patients who participated in this current study and therefore this issue is worthy of further studies.

Multi-professional team working is recommended in the literature to help improve phosphate management, which this study also supports.

Chapter 6. BIBLIOGRAPHY

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APPENDICES TO CHAPTERS 2 – 4

APPENDIX 2-1 ETHICS COMMITTEE LETTER

East London and The City NHS
Health Authority

Aneurin Bevan House, 81 Commercial Road, London E1 1RD
Telephone Number: 020 7 655 6622
Fax Number: 020 7 655 6678

Chief Renal Dietitian
Nutrition and Dietetics Department
Royal London Hospital
Whitechapel
London E1 1BB

Our Ref: RS/SB/P01092

24th October 2001

Re: P/01/092 – A randomised controlled, two part study, to evaluate the impact of different education methods to improve the patients knowledge of good serum phosphate control and to achieve the standards set by the renal association (1997) for renal bone disease

Thank you for your recent letter addressing the points of the Committee's earlier letter. I am happy to tell you that I am now able to approve this study on Chairman's action to be noted at future meeting of the Committee.

Please note the following conditions to the approval:

1. The Committee's approval is for the length of time specified in your application. If you expect your project to take longer to complete (i.e. collection of data), a letter from the principal investigator to the Chairman will be required to further extend the research. This will help the Committee to maintain comprehensive records.

2. Any changes to the protocol must be notified to the Committee. Such changes may not be implemented without the Committee or Chairman's approval.

3. The Committee should be notified immediately of any serious adverse events or if the study is terminated prematurely.

4. You are responsible for consulting with colleagues and/or other groups who may be involved or affected by the research, such as extra work for laboratories.

5. You must ensure that, where appropriate, nursing and other staff are made aware that research in progress on patients with whom they are concerned has been approved by the Committee.

APPENDIX 2.1 ETHICS COMMITTEE LETTER CONTD

6. The Committee should be sent one copy of any publication arising from your study, or a summary if there is to be no publication.

I should be grateful if you would inform all concerned with the study of the above decision.

Your application has been approved on the understanding that you comply with Good Clinical Practice and that all raw data is retained and available for inspection for 15 years.

Please quote the above study number in any future related correspondence.

Yours sincerely

P.p. Senior Administrator

Acting Chairman
ELCHA Research Ethics Committee

APPENDIX 2.2 RESEARCH AND DEVELOPMENT FUNDING APPROVAL LETTER

Barts and The London NHS
NHS Trust

2nd July 2002

Research and Development Office
4th Floor, Alexandra House
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Whitechapel
London
E1 1BB

Tel: 020 7377 7097
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Senior I Renal Dietician
Nutrition and Dietetics Department
59 Philpot Street
Whitechapel
London E1 1BB

Dear

RE: A randomised controlled two part study to evaluate the effectiveness of different education methods to achieve serum phosphate levels set by the Renal Association (1997) for haemodialysis patients.

Thank you for your Application for Funding. The Committee reviewed all projects yesterday and I am please to inform you that you have been awarded a Grant for the full amount for (INSERT DURATION OF STUDY) years. There are often issues which are picked up by the judging panel and we will be contacting you in due course to discuss these and conform the precise amount of funding available.

There are a number of conditions attached to this funding;

1) You must ensure you have Ethical Approval for the project and obtain Indemnity from the Trust R&D Office. Please send a copy of your Ethics submission to Peter Loader at the above address. At this stage you will also be asked to register your project with the Trust. If you have any queries please call Peter on 020 7377 7000 extn 2010
2) The project must start within six months of receipt of this letter. You must confirm the start date of the project in writing to me. If the project has not started within six months the Committee will decide whether funding will be withdrawn.
3) If the research is being managed through an academic unit, this will need to be covered by a research agreement. We will draw this up after I have had a chance to speak to you about the study. Please ensure that we are invoiced promptly every quarter; this is extremely important as we are not allowed to carry forward underspends from year to year. The contact in the Trust R&D Office is Phil Good (14-7717).
4) A progress report is due at the end of April 2003. If this is satisfactory funding will be approved for year two. The precise format for this report will be circulated nearer the time.
5) The Trust Communications Department is keen to publicise research going on within the Trust. We would encourage you to make contact with them and ensure the progress and findings of your work are well disseminated.

Congratulations on your award and we wish you success in the project. Please approach the R&D Office if you have any problems. We will send comments from the referees to you (subject to their permission) in the next 3-4 weeks.

Regards

Assistant Director, R&D

Review Date	3 years from approval
Approved	Trust Medicine Committee, Nursing Policy Board, Policies Working group, Trust Board
Original Distribution	**Heads of Nursing, Pharmacists**
Related Trust Policies	
Further Information	Senior Nurse Policy Development 15-7214, Assistant Director of Pharmacy 14-2770

INTRODUCTION

1. Legislation was introduced on 9 August 2000 (HSC 2000/026) detailing when medicines may be supplied and administered to patients on a direction from specified health professionals where this offers an advantage to patient care.

2. When a CNS or nurse working in a specialist area identifies the need to develop a Patient Group Direction/Protocol allowing them to administer medication without a doctors prescription he/she must gain agreement from the Lead Clinician, Head of Nursing and Directorate Pharmacist before commencing work.

3. Consult the flow chart in Appendix 1 to decide if a patient Group direction is appropriate in consultation with the Senior Nurse Policy Development or the Assistant Director of Pharmacy.

4. If agreement is reached that a patient Group direction or Protocol is appropriate complete the necessary proforma – Appendix 2.

5. The proforma must be completed with a named doctor and pharmacist and submitted to the Patient Group Directions Sub committee of Trust Medicine Committee for approval.

Patient Group Direction (PGD) for the initiation and ordering of therapy, and amendment of dosing of phosphate binders and alfacalcidol by the senior renal pharmacist and senior dietitian during a randomised controlled study

Introduction

A fully funded multi-disciplinary study is being undertaken by the renal department, to evaluate the effectiveness of different education methods and the use of nominated multiprofessional staff, to achieve serum phosphate, calcium and parathyroid hormone (PTH) levels set by the Renal Association for haemodialysis patients. During Part II of the study, patients will be randomised to receive individual advice from the pharmacist and dietitian, where the phosphate binders and related issues will be discussed in depth.
We hope to demonstrate that if our patients have a better understanding of the importance of their phosphate-restricted diet and phosphate binder medication, their serum phosphate levels will also improve.
In order to have the greatest impact during the individual advice sessions, it will be necessary to adjust the doses and/ or type of phosphate binder medication.

See Appendix 1 for detailed proposal of the phosphate binders project, and Appendix 2 for a flow chart of the study

Aim

To evaluate the effectiveness of different education methods and multi-professional staff (renal pharmacist and dietitian) on phosphate control, and thus determine the best method of educating haemodialysis patients to achieve serum phosphate levels set by the Renal Association guidelines (2002).

Objectives

1. To achieve good control of serum phosphate, calcium and PTH through a combination of phosphate restricted diet, phosphate binder medication and activated vitamin D (alfacalcidol)
2. To educate patients and thus improve their general health and quality of life
3. To maintain good communication regarding the patients phosphate control, between primary and secondary care and between patients and healthcare professionals
4. To maintain documentation, and use the positive outcomes to change our practice if indicated.
5. To generate publication data for the benefit of the wider dialysis population

Inclusion Criteria

- Stable adult patients on haemodialysis
- Age 18-75 years
- Consistent elevation of serum phosphate levels >1.8mmol/l
- Serum corrected calcium levels 2.0 – 3.0mmol/l

Exclusion Criteria

- Age <18 years or >75 years
- Serum phosphate levels <1.8mmol/l
- Serum corrected calcium levels <2.0 or >3.0mmol/l (during initial recruitment phase)
- PTH >100pmol/l during initial recruitment phase

Medicines

Phosphate binders

- Calcium salts
  - Calcichew® (calcium carbonate) tablets
  - Calcium-500 (calcium carbonate) tablets
  - Titralac® (calcium carbonate) tablets
  - Phosex® (calcium acetate) tablets
- Aluminium hydroxide
  - Alucap® capsules
  - Aludrox® mixture
- Renagel® (Sevelamer) 800mg tablets *(403mg capsules no longer in use in the Trust)*
- Fosrenol® (lanthanum carbonate) *when licensed in UK, pending approval for use within the Trust*

Legal status: POM

Dosing

- Initial dose:-
  - For tablets/ capsules : one tds with snacks or two tds with meals
  - For Aludrox® mixture 10ml tds with snacks or 20ml tds with meals
- Increase or decrease dose by increments of one tablet/ capsule (or 10ml Aludrox®) maximum per snack or meal
- Maximum total daily dose 9 capsules/tablets (or 90ml Aludrox®) of EACH preparation. Refer to renal physician if this dose is to be exceeded
- Two types of preparation can be given if required
  eg Calcichew® iii tds plus Renagel® ii tds,
  NOT two calcium preparations or two aluminium preparations

See Appendix 3 for guide to choice of phosphate binders

Vitamin D (alfacalcidol) capsules

Legal status: POM

Dosing

- Initial dose 0.25mcg daily
- Increase or decrease dose by increments of 0.25mcg or proportional equivalent
- Maximum dose 1mcg daily or 7mcg total weekly dose (to then refer to renal physicians for advice)

Procedure

This procedure will apply to patients seen by the dietitian and pharmacist in the individual advice sessions. Patients will be seen once a month for four months, in part II of the study.

All relevant information will be recorded on the clinic form (see Appendix 4), and any changes made will be used to update the Filemaker computer program.

Patients will be asked to bring in all their medication, and any medication card previously supplied. If necessary a new medication card will be supplied, containing information about the phosphate binders and alfacalcidol only.

Ordering of medicines
Any changes in therapy/ new medications required will be ordered on the "Phosphate binders project Prescription Form" (see Appendix 5) or supplied as pre-packs for patients seen at the satellite units. The patient will take the prescription forms to the Outpatient pharmacy to collect the medication.

Referral

In the following situations, the patients' medication for controlling phosphate levels should be discussed with a renal physician:-

- If corrected calcium level is *consistently (defined as "on at least 2 consecutive blood results")* >2.7mmol/l and there is no obvious explanation (eg being prescribed a calcium product or alfacalcidol)
- If aluminium levels are elevated to >2µmol/l
- If corrected calcium level is <2.0mmol/l and the patient is taking calcium-containing products and there is no problem with compliance
- If maximum doses of a combination of phosphate binders is reached, and it is felt that a higher dose is required
- If the maximum dose of alfacalcidol is reached and it is felt that a higher dose is required
- If serum phosphate level is <0.8mmol/l
- If PTH < 10pmol/l
- If PTH> 50pmol/l on at least 2 consecutive blood results, and alfacalcidol is already prescribed
- If PTH> 100pmol/l at any time

Blood monitoring

See Appendix 2 for flow chart showing ideal time to take bloods

- Serum corrected calcium and phosphate levels every month
- Serum PTH level ideally at month 0,5 and 10 of the study
- Serum aluminium level at 6 monthly intervals (at least once during the 4 months of Part II of the study)
- Serum aluminium level ideally at 3 monthly intervals for all patients taking oral aluminium *(no patient whose ferritin is < 100mcg/l should have an aluminium level >2.2micromol/l)*

Training requirements and Assessment Criteria:

The practitioners (senior dietitian and pharmacist) should have a good working knowledge of prescribing issues in renal patients, particularly with respect to the management of hyperphosphataemia.

Essential reading material:-

1. Management of the renal patient: Experts' recommendations and clinical algorithms on renal osteodystrophy and cardiovascular risk factors.
   Editors: Cannata-Andia J, Passlick-Deetjen J, Ritz E
   Nephrology Dialysis Transplantation. Volume 15 (2000) Supplement 5
   Note: The medical expert group that wrote the guidelines, includes Professor John Cunningham (the internal referee for the project)
2. Altmann P. Calcium and phosphate in renal failure: the disease. *Br J Renal Medicine* Winter 2001; 6-9.
3. Altmann P. The control of calcium and phosphate in renal failure. *Br J Renal Medicine* Spring 2002; 6-9.

The practitioners should be assessed as competent by the consultant nephrologist. This will involve checking during the first two clinic sessions that recommendation made by the practitioner are appropriate. At month 2-3 of the individual advice sessions, there will be a review of the decision-making process, in liason with the consultant nephrologist.

Documentation:

- Phosphate binders clinic form (Appendix 4)
- Phosphate binders project Prescription Form (Appendix 5)
- Letter to GP regarding recruitment of patients into study (Appendix 6)
- The "Filemaker" computer system for the Renal Unit, will have patients records individually updated when appropriate
- Letter to GP regarding dosing/medication changes in intensive clinic (*Appendix 7 – this will be designed when the Filemaker system has been amended*)
- Medication cards for patients - template designed specifically for phosphate binders and alfacalcidol(Appendix 8)

Monitoring and Audit

Audit and monitoring of clinical effectiveness of the "individual advice sessions" part of the study:-

- patient satisfaction with the service provided
- evaluate impact of the individual advice sessions on:-
  - adherence to phosphate-restricted diet
  - patients' compliance with and good understanding of phosphate binder medication
  - blood results
- impact of individual advice compared with group teaching

Review date
To be reviewed upon completion of study

Patient Group Direction (PGD) for the initiation and ordering of therapy, and amendment of dosing of phosphate binders and alfacalcidol by the senior renal pharmacist and senior dietitian during a randomised controlled study

Name of Pharmacist: xxxxxxx RPSGB number: xxxxx

Name of Dietitian xxxxxxxx Dietitian Registration number: xxxxxxx

Assessment criteria:

- Demonstrates knowledge of the legal aspects regarding the prescribing and administration of medicines (particularly regarding phosphate binders and vitamin D) and understands the differences between POM's Ps and GSL medicines — Yes
- Can state their professional responsibilities with regard to administration of phosphate binders and alfacalcidol against the PGD — Yes
- Can state the professional responsibilities of other multi-disciplinary team members with regard to the PGD — Yes
- Can explain the individual indications for administering phosphate binders and alfacalcidol against the PGD — Yes
- Is observed by the Consultant nephrologist during the first two clinic sessions, at initiating or amending doses, and ordering phosphate binders and alfacalcidol, under the PGD, — Yes
- Can demonstrate the absolute and relative contraindications for the phosphate binders and alfacalcidol in the PGD — Yes
- Demonstrates knowledge of the side effects and interactions of phosphate binders and alfacalcidol in the PGD — Yes
- Demonstrates the knowledge of the maximum doses that may be administered for the phosphate binders and alfacalcidol in the PGD — Yes
- Specifically understands the conditions of responsibility for their profession., as described in the RPSGB Code of Ethics and the Dietitians Board Code of Conduct, for the pharmacist and dietitian respectively — Yes
- Demonstrates the ability to maintain accurate records — Yes

Assessors: Date:_____

Pharmacist:_____ Date:_____

Dietitian: _____ Date: _____

Staff covered by the Group Direction:

xxxxxxxxx
Names and titles of protocol development team: xxxxxxxxx
Named Assessors: **Xxxxxxxxx, xxxxxxxxxx**
Date direction commences: *At the start of Part II of the project (estimated to be December 2003)*
Date direction expires: Upon completion of the project

Submitted by: xxxxxxxxxx
Ward/department: Pharmacy

Contact number: xxxxxxxxxx

Clinical Director/Lead Clinician signature:_____ Date: _____

(print name) xxxxxxxxx

Head of Nutrition and Dietetics signature: _____ Date: _____
(print name)
xxxxxxxxxx

Chief Pharmacist signature: _____ Date: _____
(print name)
xxxxxxxxxx

Chair Patient Group
Direction Committee: _____ Date: _____
(print name)

- Calcium carbonate should generally be regarded as the phosphate binder of choice. The best preparation is Calcichew (for those who prefer to chew rather than swallow) or Calcium 500 (for those who prefer to swallow rather than chew).

- Calcium acetate is a more expensive alternative with a different GI side effect profile.

- *Aluminium hydroxide or Renagel® would be considered as an adjunct or substitute if*

  - Calcium carbonate proves ineffective in controlling hyperphosphataemia.
  - Calcium carbonate leads to unacceptable hypercalcaemia. This is quantified as serum calcium > 2.7 mmol/L on more than one occasion and/or > 2.85 mmol/L on a single occasion in the absence of another cause of hypercalcaemia
  - Calcium carbonate leads to unacceptable GI disturbance

- Consideration should be given to the likelihood of aluminium toxicity developing. The major risk factors appear to be:

  - High aluminium hydroxide dosing.
  - Protracted therapy.
  - Absence of residual renal function.
  - Low PTH.

- The use of aluminium hydroxide should, as far as possible, be subject to the following provisos:
  - The dose should be the lowest that is compatible with adequate efficacy.
  - Serum aluminium must be monitored at six monthly intervals.
  - Great caution should be exercised in regard to aluminium hydroxide use in patients for whom a prolonged period of dialytic treatment is likely (younger patients, those without co-morbidity, patients unlikely to be transplanted).

- Renagel® is appropriate in those patients unable to take an efficacious dose of calcium carbonate and in whom there is significant risk of aluminium toxicity as judged by the above considerations.

N.B. Many dialysis centres in the UK and virtually all in the USA have ceased prescribing aluminium on grounds of safety.

These indications for Renagel® are deliberately conservative and may need to be extended if calcium carbonate therapy is established as a cause of accelerated soft tissue calcification.

Algorithms

Phosphate raised – see algorithm 1
Phosphate same – see algorithm 2
Phosphate low – unlikely scenario in this group of patients, REFER TO CONSULTANT

Primary targets

1. **To achieve calcium and phosphate levels within the target range (Cor Ca 2.2-2.65mmol/l and PO4 0.8-1.8mmol/l)**
2. **To adjust dosing of alfacalcidol if PTH level falls outside the target range (PTH 5-20pmol/l)**

Summary table showing effects of phosphate binders and vitamin D on levels of corrected calcium, phosphate and PTH

Drug	*Corrected Calcium level*	*Phosphate level*	*PTH level*
Calcium carbonate/ acetate	↑	↓	↓↓
Aluminium hydroxide	→	↓	↓
Sevelamer	→	↓	↓
Alfacalcidol	↑	↑	↓↓↓

APPENDIX 2.4.1 PROTOCOL ALGORITHM 1

Algorithm 1

Note 1 "consistently" is defined here as "on at least 2 consecutive blood results"
Note 2 All referrals listed in the algorithms, are to the renal physicians

Phosphate ↑ (> 1.8mmol/l)

Corrected Calcium ↓ **(<2.2mmol/l)**
Start/ ↑ dose calcium-containing phosphate binder

PTH <10pmol/l (unlikely scenario)
Stop alfacalcidol

PTH 10-20pmol/l
Start/ maintain dose alfacalcidol

PTH >20pmol/l
Start/ ↑ dose alfacalcidol (only after achieving phosphate level in target range)

Refer
- PTH <10pmol/l
- PTH >50pmol/l
- Corrected Calcium <2mmol/l
- If max dose alfacalcidol reached
- High aluminium level

Corrected Calcium in normal range (2.2-2.65mmol/l)
Start/ ↑ dose phosphate binder.
If corrected calcium is consistently at the upper end of the normal range, consider switch to non-calcium phosphate binder (aluminium or sevelamer)

PTH 10-20pmol/l
Maintain dose alfacalcidol

PTH >20pmol/l
Start/ ↑ dose alfacalcidol (only after achieving phosphate level in target range)

Refer
- PTH <10pmol/l
- PTH >50pmol/l
- If max dose alfacalcidol reached

Corrected Calcium ↑ **(>2.65mmol/l)**
Stop/ ↓ dose calcium-containing phosphate binder

Start/ ↑ dose non-calcium phosphate binder (aluminium or sevelamer)

Stop alfacalcidol if:-
EITHER
Corrected Calcium > 3.0mmol/l

OR

Persistent Corrected Calcium > 2.7mmol/l after reduction of dose of calcium-containing phosphate binder

Refer
- PTH <10pmol/l
- PTH >50pmol/l
- High aluminium level
- Corrected calcium level consistently >2.7mmol/l, with no obvious explanation

APPENDIX 2.4.2 PROTOCOL ALGORITHM 2

Note 1 "consistently" is defined here as
"on at least 2 consecutive blood results"
Note 2 All referrals listed in the algorithms,
e to the renal physician

Algorithm 2

Phosphate in normal range
(0.8 – 1.8mmol/l)

Corrected Calcium ↓ **(<2.2mmol/l)**

Start/ ↑ dose calcium-containing phosphate binder

↓ dose non-calcium containing phosphate binder if appropriate

Start/ ↑ dose alfacalcidol, if both Corrected Calcium and Phosphate levels are at lower end of target ranges

Refer

- PTH <10pmol/l
- PTH consistently >50pmol/l
- Corrected Calcium <2mmol/l
- If max dose alfacalcidol reached

Corrected Calcium in normal range (2.2-2.65mmol/l)

PTH 10-20pmol/l

No change

PTH >20pmol/l

Start/ ↑ dose alfacalcidol (only after achieving phosphate level in target range)

Start/ ↑ dose calcium-containing phosphate binder

Refer

- PTH <10pmol/l
- PTH >50pmol/l
- If max dose alfacalcidol reached

Corrected Calcium ↑ **(>2.65mmol/l)**

PTH 10-20pmol/l

↓ dose calcium-containing phosphate binder initially

↓ dose alfacalcidol also, if corrected calcium level is consistently >2.7mmol/l

PTH >20pmol/l

As above

Refer

- PTH <10pmol/l
- PTH consistently >50pmol/l
- Corrected calcium level consistently >2.7mmol/l, with no obvious explanation

APPENDIX 2.5 ORIGINAL PHOSPHATE KNOWLEDGE QUESTIONNAIRE

ID No:	Group:	Date:

Monitoring blood phosphate levels – a patient survey

Please complete the following questionnaire as fully as possible.
If you feel unable to answer any question then leave it and pass onto the next one.
Please return the questionnaire even if you are unable to complete it.

Q1. Which gender are you? (Please circle):

Female / Male

Q2. Are you (please circle):

a. Under 18yrs
b. 18-29 years
c. 30-39 years
d. 40-49 years
e. 50-59 years
f. 60-69 years
g. 70-79 years
h. 80-89 years
i. Over 89 years

Q3 Are you (please circle):

a. White British
b. White Irish
c. White other, please state .....
d. Black British
e. Black Caribbean
f. Black African
g. Black other, please state.....
h. Indian
i. Bangladeshi
j. Pakistani
k. Indian British
l. Bangladeshi British
m. Pakistani British
n. Indian African
o. Indian Carribean
p. Asian other, please state.....
q. Chinese
r. Chinese other, please state.....

If you feel that none of the above describe your ethnic origin please enter it in the space below:

.....

Q4 What is your preferred language for (please state):

Reading .....

Writing ....

Q5 How long have you been on dialysis? (please circle)

Less than one year / 1-2 years / 2-3years / 3-4 years / 5 years

If longer than five years, please state how many .....

Q6 i) Are you told what your blood phosphate level is each month? (Please circle)

a. Yes now go to Q7 b. No c. Sometimes
d. Don't know

ii) Do you ask the staff what your blood phosphate level is each month? (Please circle)

a. Yes b. No c. Sometimes

Q7 What is the **acceptable range** for blood phosphate levels (mmol/l) ? (please circle)

a. 0.1-0.8 **b. 0.8-1.8** c. 1.7-2.5 d. 2.5-3.5
e. Don't know

Q8 Which of these are known as phosphate binders? (circle as many as you like)

a. Alu – caps b. Simvastatin **c. Calcichew**
d. Calcium Carbonate e. Don't know f. None of these

Q9 Do you take any phosphate binders? (please circle)

Yes / No

If no, then go to Q13

Q10 Which phosphate binder medications do you take? Please give their names below:

OR, circle:
None / Don't know

Q11 On average, when do you take your phosphate binders? (Please circle one answer only):

a. 30 minutes before meals b. During your meal c. The time varies
d. 10 minutes before meals e. Just after your meal
f. Whenever it is convenient **g. mmediately before meals**
h. 30 minutes after your meal i. Don't know

Q12 On average, do you take your phosphate binders as prescribed (Please circle one answer only):

a. Always (never miss a dose)

b. Fairly regularly (sometimes miss a dose)

c. Occasionally (frequently miss a dose)

d. Not at all (never take a dose)

e. Don't know

Q13 Which of these foods are **RICH** in phosphate? Please circle below as many foods as you wish.

a . Crisps **b. Nut** c. Pasta d. Fruit
e. Yogurt **f. Chocolate** **g. Cheese** h. Vegetables
i. None of these j. Don't know

Q14 If you have a high blood phosphate level what is the most likely symptom that you will experience? (please circle one answer only)

a. Swollen ankles
b. **Itchy skin**
c. Headaches
d. Vomiting
e. None of these
f. All of these
g. Don't know

Q15 Which of these drinks are **RICH** in phosphate? Please circle below as many drinks as you wish.

a. Coffee b. **Ovaltine** c. Pure fruit juice d. **Milk** e. Water
f. Tea g. Wine h. Squash i. None of these
j. All of these

Q16 What parts of your body can be harmed by poor phosphate control in the long term? (please circle as many as you wish)

a. **Heart**
b. **Eyes**
c. Liver
d. **Bones**
e. **Skin**
f. None of these
g. All of these
h. Don't know

Q17 Which of these foods are **LOW** in phosphate? Please circle below as many foods as you wish.

a. **Fruit** b. **Vegetables** c. **Pasta** d. Cheese e. Chocolate
f. **Crisps** g. Yogurt h. Nuts i. None of these
j. All of these k. Don't know

Q18 How can your blood phosphate level be better controlled? (Please circle as many as you wish)

a. **By eating a low phosphate diet**
b. **By taking phosphate binders**
c. By having less dialysis
d. By eating a high phosphate diet
e. By not taking phosphate binders
f. **By having more dialysis**
g. All of these
h. None of these
i. Don't know

Q19 Which of these drinks are **LOW** in phosphate? Please circle below as many as you wish.

a. **Tea**
b. **Wine**
c. **Squash**
d. Milk
e. **Water**
f. Coffee
g. Ovaltine
h. **Pure fruit juices**
i. None of these
j. All of these
k. Don't know

MANY THANKS FOR COMPLETING THIS QUESTIONNAIRE

APPENDIX 2.6 REVISED PHOSPHATE KNOWLEDGE QUESTIONNAIRE

ID No:	Group:	Date:

Monitoring phosphate knowledge – a patient survey

Q1 Are you told what your blood phosphate level is each month? (Please circle)

1. Yes 2. No 3. Sometimes 4. Don't know

Do you ask the staff what your blood phosphate level is each month? (Please circle)

1. Yes 2. No 3. Sometimes

Score: **none**

Q2 Do you know what your blood phosphate level should be?

1. **Yes** 2. No

Answer:……**0.8 – 1.8**

Score: **1** for a correct value within range score: **2** for correct range **Total: 2**

Q3 What symptoms might you experience if you have a high blood phosphate level?

Answer: - **itchy skin**
- **red eyes**

Score **1** for each correct answer **Total: 2**

Q4 Which parts of your body can be affected by poor phosphate control in the long term?

Answer: **- bones stomach heart lungs blood vessels skin eyes**

Score **1** for each correct answer **Total: 7**

Q5 Do you know how your blood phosphate level can be controlled?

Answer: Yes No

- Taking phosphate binders as prescribed

- Getting adequate dialysis

- **Eating a low phosphate diet**

Score **1** for each correct answer **Total: 3**

Q6 Do you take any medicines for controlling phosphate? (also called phosphate binders)

1. Yes (If yes, which ones?) 2. No. (If no, go to Q 10)

Answer……
……
……

Score: **none**

Q7 On average, when do you take your phosphate binders? (Please circle one answer only):

1. 30 minutes before meals
2. During your meal
3. The time varies
4. 10 minutes or less before meals
5. Just after your meal
6. Whenever it is convenient
7. Immediately before meals
8. 30 minutes after your meal

Score **1**

Q8 Do you know whether this is the correct time for you to take your phosphate binders?

Answer……**Yes**……
……
……
……Score: **none**……

Q9 On average, do you take your phosphate binders as prescribed?
(Please circle one answer only)

1. **Always (never miss a dose)**
2. Fairly regularly (sometimes miss a dose)
3. Occasionally (frequently miss a dose)
4. Not at all (never take a dose)

Score: **none**

Q10 Please specify for each of the following foods, whether the food can be eaten freely, in moderation or should be avoided as part of a low phosphate diet. (Please circle below)

	Freely	**Moderation**	**Avoid**
Cornflakes	**1**	2	3
Muesli	1	2	**3**
White bread/rolls	**1**	2	3
Liver	1	2	**3**
Cheese	1	**2**	3
Nuts (as a snack)	1	2	**3**
Bony fish	1	2	**3**
Yogurt	1	**2**	3
Pasta	**1**	2	3

Score: **1** for each correct answer **Total: 9**

Q11 For each of the following drinks, please specify whether each drink, within your fluid allowance, can be consumed freely, in moderation or should be avoided if following a low phosphate diet. Please circle below

	Freely	**Moderation**	**Avoid**
Ovaltine	1	2	**3**
Milk	1	**2**	3
Water	**1**	2	3
Tea	**1**	2	3
Squash	**1**	2	3
Fizzy Drinks	1	**2**	3

Score: **1** for each correct answer **Total: 6**

GRAND TOTAL: 30

APPENDIX 3.1 LOW PHOSPHATE DIET SHEET

Low phosphate diet sheet

At present your phosphate level is ..... mmol/l (normal range: 0.8 - ..... mmol/l)
It is important to try and control these levels. Since phosphate is present in the food we eat the table below is a guide of common foods classed as suitable foods to eat and foods to avoid. Your dietitian can discuss in more detail.

Food Item	Low phosphate Foods TO HAVE	High Phosphate Foods TO AVOID
Dairy products	Cow, soya or goats milk	Evaporated or condensed milk, milk powder
	• Limit milk to 300ml (1/2 pint) per day; also include milk products in this like yoghurt, custard, milk in sauces and puddings. • Cheese, not more than 120g (4 ounces) per week. One ounce of cheese is the size of a small matchbox.	
Eggs	• Limit eggs to 4 eggs per week. If you are vegetarian then this amount can be discussed with the dietitian.	
Meat, fish	Beef, lamb, pork, chicken, white fish, mackerel, salmon, tuna, Quorn, tofu, beans and lentils	Game, offal, fish with edible bones, prawns, scampi, white bait, patés made from offal All nuts and nut products
Breads and cereals	Cornflakes, porridge oats, Rice Crispies, Weetabix, Shredded Wheat Rice, pasta, white or wholemeal bread.	All Bran, Ready Brek, bran flakes, cereals with nuts or seeds. Granary bread or bread with nuts or seeds.
Drinks	Tea, coffee*, fruit squashes, fizzy drinks (cola only 200ml per day)	Ovaltine, Super malt, Horlicks, Drinking chocolate, Complan, Build Up, Nourishment, Milo

- Remember if you are prescribed phosphate binders for example Calcichew, Renagel or Alucaps, you must take them **5 - 10 minutes before** your meals. If you are prescribed calcium acetate take them with your meals.

- If you take iron tablets these must be taken **after food** to allow both the iron tablets and phosphate binders to work properly.

- Avoid these foods if following a low potassium diet.

- Any questions please contact the renal dietitians on 0207 377 7735.

APPENDIX 3.2 PATIENT MEDICATION CARD

MEDICINES		DOSE	FREQUENCY	SPECIAL INSTRUCTIONS	POSSIBLE COMMON SIDE-EFFECTS	PURPOSE	CONTINUE OR SHORT COURSE
NAME(S)	SAMPLE						
CALCIUM CARBONATE 500mg TABLETS (CALCICHEW®)			THREE times a day	5 – 10 minutes before meals Chew or dissolve in mouth before swallowing	**Constipation**	To reduce, and keep within the normal range, the amount of phosphate in your blood.	**Continue**
CALCIUM CARBONATE 500mg TABLETS (CALCIUM 500®)			THREE times a day	5 – 10 minutes before meals Swallow whole	**Constipation**		
CALCIUM ACETATE TABLETS (PHOSEX ®)			THREE times a day	5 – 10 minutes before meals Swallow whole	**Constipation**		
CALCIUM CARBONATE TABLETS (TITRALAC®)			THREE times a day	5 – 10 minutes before meals Swallow whole	Constipation		
ALUMINIUM HYDROXIDE CAPSULES (ALUCAPS®)			THREE times a day	5 – 10 minutes before meals Swallow whole	Constipation		
ALUMINIUM HYDROXIDE LIQUID (ALUDROX®)				5 – 10 minutes before meals	Constipation		
SELEVAMER HYDROCHLORIDE 800mg TABLETS (RENAGEL®)			THREE times a day	5 – 10 minutes before meals Swallow whole	Diarrhoea, nausea, vomiting, indigestion, constipation		
ALFACALCIDOL 0.25 microgram CAPSULES			EACH MORNING	None	None	To increase your blood calcium levels and keep it normal	

APPENDIX 3.3 PATIENT INFORMATION LEAFLET

A randomised controlled two part study to evaluate the effectiveness of different education methods to achieve serum phosphate levels set by the Renal Asssociation (2002) for haemodialysis (HD) patients

Invitation

You are invited to take part in a research study. Before you decide if you want to take part or not, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends and relatives if you wish. Ask us about anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part. If you would like to take part please ask the dialysis nurse to contact the renal dietitian or the pharmacist. If you do not get in touch then the Dietitian or the Pharmacist will contact you in approximately two weeks time.

What is the purpose of the study?

Improving the phosphate control in haemodialysis patients is extremely important as continuous high phosphate levels can lead to renal bone disease. Renal bone disease can be very painful and lead to difficulty in movement and therefore reduce the quality of life.

Phosphate levels are controlled by following a strict diet and drug regime. Previous audits carried out on the unit indicate a large number of patients have continuous high phosphate levels. Studies from other dialysis units have obtained similar results. The reasons for poor control include lack of understanding of the phosphate restricted diet and phosphate binder regime.

The purpose of this study is to improve patient's knowledge and understanding about their phosphate control using different teaching methods and identifying the most effective teaching method to help control phosphate levels.

Why have I been chosen?

The study is open to all haemodialysis patients with blood phosphate levels higher than the acceptable range.

Do I have to take part?

It is up to you to decide whether or not to take part. If you decide to take part you will be asked to sign a consent form. You will be free to withdraw at any time without giving a reason. This will not affect the care you receive.

What will happen to me if I decided to take part?

After checking you are suitable to take part in the study, you will be asked to complete a consent form.

You will continue to have your blood taken monthly which includes calcium and phosphate levels. Your parathyroid hormone (PTH) levels are measured routinely by haemodialysis staff twice a year. As part of this study we require two additional PTH levels which will be obtained from your routine blood samples at the beginning and end of the study.

At the start of the study you will be randomly assigned to your group within the study - this is like tossing a coin to see which group you will end up in. You will not be able to choose which group you would like to be in.

You will also be interviewed by a member of the research team to determine your current phosphate knowledge during a dialysis session.

Part I:

Groups 1 + 2

These patients will receive a one hour group advice session run by the renal dietitian and renal pharmacist. These sessions will take place at Barts, Royal London or Whipps Cross. (Refreshments will be provided)

We are prepared to do separate teaching sessions in foreign languages if necessary

Approximately two weeks after the group advice session patients will be interviewed again to determine their current phosphate knowledge.

Groups 3 + 4

These patients will receive individual advice by the renal dietitian and the renal doctor on the unit or in clinic as normal.At the end of Part I these patients will be interviewed again to determine their current phosphate knowledge.

Part II:

Groups 1 + 3

These patients will be seen by the renal dietitian and a renal pharmacist at their dialysis unit to focus on phosphate control. You will be seen once a month for four months. You may have your phosphate binders changed or the dose of the binders altered.

Your GP will be informed of any changes.

Groups 2 + 4

These patients will receive individual advice by the renal dietitian and the renal doctor on the unit or in clinic as normal. At the end of part II all patients will be interviewed again to determine their current phosphate knowledge.

The results from the phosphate questionnaires and your monthly bloods will help us to determine which method of teaching is the most effective and will be incorporated into the routine care of the patients.

What are the physical risks and benefits of taking part?

There are no physical risks in taking part in this study. All methods of teaching will provide the same information but will differ only in the way they are presented. We hope that the most effective method will be identified at the end of the study and will be incorporated into the routine care of the patients.

Will my details remain confidential?

All information collected about you during the course of the study will be kept strictly confidential. Any published data will not have your name on it. We may wish to take photographs of group teaching sessions or individual clinic sessions, this will only be done with your consent.

Will my GP be informed?

Yes.

How can I get more information?

The investigators (dietitian and the pharmacists) conducting the study can provide you with any additional information you require. You will be able to contact an investigator to discuss your concerns and /or to get help:

What happens if something goes wrong?

We believe that this study is safe and do not expect you to suffer any harm or injury because of your participation in it. However, *Barts and The London NHS Trust* has agreed that if your health does suffer as a result of your being in the study then you will be compensated. In such a situation, you will not have to prove that the harm or injury which affects you is anyone's fault. If you are not happy with any proposed compensation, you may have to pursue your claim through legal action.

APPENDIX 3.4 WRITTEN CONSENT FORM:

Title of research proposal:
A randomised controlled, two part study, to evaluate the effectiveness of different education methods to achieve serum phosphate levels set by the Renal Association (2002) for haemodialysis patients.

REC Number: P/01/092

Name of Patient/Volunteer (Block Capitals):

Address:

- The study organisers have invited me to take part in this research. ☐
- I understand what is in the leaflet about the research. I have a copy of the leaflet to keep. ☐
- I have had the chance to talk and ask questions about the study. ☐
- I know what my part will be in the study and I know how long it will take. ☐
- I know how the study may affect me. I have been told if there are possible risks. ☐
- I know that the local East London and The City Health Authority Research Ethics Committee has seen and agreed to this study. ☐

- I understand that personal information is strictly confidential: I know the only people who may see information about my part in the study are the research team or an official representative of the organisation which funded the research. ☐
- I understand that my personal information may be stored on a computer. If this is done then it will not affect the confidentiality of this information. All such storage of information must comply with the 1998 Data Protection Act. ☐
- I know that the researchers will tell my general practitioner (GP) about my part in the study. ☐
- I freely consent to be a subject in the study. No-one has put pressure on me. ☐
- I know that I can stop taking part in the study at any time. ☐
- I know if I do not take part I will still be able to have my normal treatment. ☐
- I know that if there are any problems, I can contact:

Miss.....

Tel. No. .....…… Bleep No./Ext / Pager No .....

Patient's/Volunteer's: Signature .....

Witness's Name .....

Witness's Signature: .....

Date .....

The following should be signed by the Investigator responsible for obtaining consent

As the Investigator responsible for this research or a designated deputy, I confirm that I have explained to the patient/volunteer named above the nature and purpose of the research to be undertaken.

Investigator's Name: .....……..

Investigator's Signature: .....…….. Date: .....

APPENDIX 3.5 COMPLIANCE WITH THE DATA PROTECTION ACT

INTRODUCTION

The Barts and The London NHS Trust is obliged by law to notify the Data Protection Commissioner of the reasons for holding all relevant filing systems (electronic and paper) that contain personal data about identifiable living individuals, whether they be staff, contractors or patients. Failure to do so could lead to prosecution under the Data Protection Act 1998.

Currently, only computer applications are recorded. There are a large number of other filing systems and databases, which are not yet registered under the act. This survey is therefore being conducted to establish the details of all applications where personal data is held.
A list of computer applications currently registered by staff in your directorate, which hold details about individuals, is attached. Please amend the list as follows:

- Tick applications still in use (adding contact details if missing).
- Delete applications no longer in use and where the data has been destroyed.

Add new applications by completing a copy of the attached form for each application. (You need not include use of PAS, PRIDE or Document Management System run by the JEC.)

For paper filing systems structured by name or number so that information about an individual can be easily referenced, you are required to complete a copy of the attached form for each filing system.
NB Please complete a separate form for each storage location for Health Records.
Additional forms can be copied. They are available from the shared folders on E-Mail *??where??* or can be obtained from John Fowler, the Data Security Manager, on ext 14-2063, or Penelope Baker, Modern Records Manager, on ext 14-2409.

RETURN OF INFORMATION

Completed listings and forms for new electronic and all paper systems should be returned to John Fowler, Information Security Manager, Whitechapel: Email <Fowler John> as soon as possible.

Further advice and guidance on how to complete the form can be obtained from John Fowler, ext 14-2063, or Penelope Baker, ext 14-2409.
- to sign

CHIEF EXECUTIVE

Trust Secretary

COMPLIANCE WITH THE 1998 DATA PROTECTION ACT
GUIDANCE NOTES FOR THE COMPLETION OF DPAFORM2.

SYSTEMS TO BE RECORDED

Data is deemed to be personal if:

- it relates to a living individual and can be identified as such
- it can be retrieved by a direct reference to that individual or by inference allowing the data to be associated with an individual - ie any file coded by personal reference number or ***containing*** information such as name or address or postcode, date of birth, sex.

For Health Records, a separate form (marked HR) must be completed for each location where records are stored.

COMPLETION OF THE *??title??* FORM *(The paragraph numbers relate to the item number on the form)*

1. DIRECTORATE/DEPARTMENT/SECTION:

   This should be the directorate and department name as recorded in the internal telephone directory (and section if relevant).

2. CONTACT DETAILS

   Give the name, job title and phone number (also internal email if possible) of the person to be contacted for follow-up information about this database/set of records.

3. NAME OF APPLICATION

   The local name by which the database or set of records is known. For manual (paper) sets of records without a 'title', mark the box N/A.

4. TYPE

   For records held on computer, eg databases, enter E (electronic).

   For sets of paper records/filing systems, enter M (manual).

4a Enter HR for Health Records. Otherwise leave blank.

5. SIZE

For computer/electronic records, enter number of records/files in the database/system.

For paper/manual records, state the number of files or approximate linear footage of shelf space occupied.

6. ARRANGEMENT/SORT CODE

For computer/electronic records, state the name of key indexing field/data.

For paper/manual records, state how the records are organised – e.g. by name, number or subject (NB if the filing system is organised by subject, it may not be subject to the provisions of the Data Protection Act)

7. PURPOSE

Please state the purpose to which this data is put – eg Research, Accounting, Personnel Administration, etc.

8. STORAGE OF DATA

For electronic records, state workstation number (WS no.) of computer holding database or state if networked.

For manual files (particularly the Health Record), state where they are stored.

Note: In order to comply with Principle 7 of the 1998 Data Protection Act, all records must be stored securely (see Appendix A).

9. TYPE OF DATA

Please give a full description of the types of personal data that you hold, by identifier - ie name, address, telephone number, date of birth, sex, etc. You should also give details of other data held - eg test results, medical details, opinion data in free form text fields (eg medical opinions, health assessments, etc).

Note : It is important that Principle 4 of the 1998 Data Protection Act (see Appendix A) is applied to such fields. It should be remembered that the Data Subject can request to see a copy of this data **at any time** and disclosure is, in most circumstances, **compulsory**.

Put the date of the first document/ record, if known.

10. SOURCE OF DATA

Please state the source of any data added locally to the file. This could be from the data subjects themselves, relatives, friends, other BLT staff, police, other health care workers in other trusts, GPs etc.

11. DATA DISCLOSURE

It is particularly important to record to whom this data disclosed, whether it be to BLT staff or outside individuals and organisations. You must also state whether any data is passed outside the European Economic Area (EEA)– eg research data given to pharmaceutical companies based outside of the EEA.

The EEA consists of the 15 European Union Member States plus Iceland, Norway and Liechtenstein. Special consideration will be required for processing carried out elsewhere.

RETURN OF FORMS

Completed forms should be returned to Information Security Manager

Further advice and guidance on completion of the form can be obtained from xxxx ext xxxxx, or xxxx, ext xxxx

APPENDIX 3.6 LETTER TO GENERAL PRACTITIONER

Nutrition and Dietetic Department,
Directorate of Nursing and Therapies,
The Royal London Hospital,
Whitechapel
London E1 1BB

Tel:
Fax:
Switchboard:

Date:

Dear Dr .....

Re: D.O.B.

The above named patient has been recruited to participate in a clinical study:

A randomised controlled, two part study, to evaluate the effectiveness of different education methods to achieve serum phosphate levels set by the Renal Association (2002) for haemodialysis (HD) patients.

Please see the attached "**General information and an invitation to participate in the study**"leaflet for more information.

During the course of the study the principal investigators may change:-
i) the dose or type of phosphate binders
ii) the dose of alfacalcidol
If this is the case you will be notified.

The principal investigators are :-
XXXXXX (Senior Renal Dietitian)
XXXXXX (Senior Renal Pharmacist)

XXXXXX (Renal Consultants) / Project Supervisors)

If you have any queries please do not hesitate to contact us

.....
Signature (of a Principal Investigator)

APPENDIX 4.1: PILOT STUDY-PD PATIENT POPULATION AND PHOSPHATE KNOWLEDGE QUESTIONNAIRE RESULTS

SECTION A: PATIENT DEMOGRAPHICS

A1) Gender
Female: 10 (48%) ;
Male: 11 (52%)

A2) Age
a) Under 18yrs 1 (5%) b) 18-29 years 2 (9%)
c) 30-39 years 1 (5%) d) 40-49 years 3 (14%)
e) 50-59 years 5 (24%) f) 60-69 years 5 (24%)
g) 70-79 years 2 (9%) h) 80-89 years 2 (11%)
i) over 89 years 0 (0%)

A3) Ethnicity

a) White British 11 (52%) b) Black Caribbean 3 (14%) c) Indian 1 (5%)
d) Bangladeshi 1 (5%) e) Pakistani 1 (5%) f) Indian British 2 (9%)
g) Other: Greek Cypriot 1 (5%) Mauritian 1 (5%)

A4) Preferred Language:-
Reading ..... English 19 (90%) ; Malayalam 1 (5%) ; Bengali 1 (5%)

Writing .... English 19 (90%) ; Malayalam 1 (5%) ; Bengali 1 (5%)

A5) Length of time on dialysis

a) Less than one year 9 (43%) b) 1-2 years 3 (14%) c) 2-3years 4 (19%)
d) 3- 4 years 0 (0%) e) 5 years 0(0%)

If longer than five years, please state how many ...5 (24%)

SECTION B: CURRENT PRACTICES IN THE DIALYSIS UNIT

B1 i) Are you told what your blood phosphate level is each month?

a) Yes 2 (9%)* b) No 10 (48%) c) Sometimes 5 (24%)
d) Don't know 4 (19%)
*one patient stated that they asked

ii) Do you ask the staff what your blood phosphate level is each month?
a. Yes b. No c. Sometimes

B2 Do you take any phosphate binders? Yes 17 (81%) / No 4 (19%)

B3 Which phosphate binder medications do you take? Please give their names below:
only 18 answered

Calcichew 9 (50%) Alu –cap 1 (5%) Calcium Carbonate 3 (17%)
Renagel 2 (11%)
OR, circle:
None / Don't know 3 (17%)

SECTION C: PATIENT KNOWLEDGE ON PHOSPHATE MANAGEMENT AND HEALTH IMPLICATIONS
Nb Correct answers are in bold text

C1 What is the acceptable range for blood phosphate levels (mmol/l)?

a. 0.1-0.8 **b. 0.8-1.8** 1(5%) c. 1.7-2.5 d. 2.5-3.5
e. Don't know 20 (95%)

C2 Which of these are known as phosphate binders?

a. Alu – caps 3 (14%) b. Simvastatin **c. Calcichew** 14 (67%)
d. Calcium Carbonate 6 (29%)

e. Don't know 3 (14%) f. None of these

C3 If you have a high blood phosphate level what is the most likely symptom that you will experience?
Some patients gave > 1 answer
a. Swollen ankles 3 (14%) b) **Itchy skin** 10 (48%) c) Headaches 1 (5%)
d) Vomiting 1 (5%) e) None of these f) All of these
g) Don't know 8 (38%)

C4 What parts of your body can be harmed by poor phosphate control in the longterm?

a. **Heart** 5 (24%) b) **Kidneys** 5 (24%) c) Liver 4 (19%)
d) **Bones** 11 (52%) e) **Skin** 4 (19%) f) **Eyes** 2 (10%)
g) None of these h) All of these i) Don't know 4 (19%)

C5 How can your blood phosphate level be better controlled?

a. **Eating a low phosphate diet** 15 (71%)
b. b) **Taking phosphate binders** 15 (71%)
c. Having less dialysis 1 (5%)
d.Having a high phosphate diet 1 (5%)
e) Not taking phosphate binders
f) **By having more dialysis** 4 (19%)

g) All of these h) None of these i) Don't know 4 (19%)

SECTION D: PATIENTS' DIETARY PHOSPHATE KNOWLEDGE

D1 Which of these foods are **RICH** in phosphate?

a. Crisps 9 (43%) **b. Nuts** 12 (57%) c. Pasta 2 (10%)
d. Fruit 6 (29%) **e. Yogurt** 6 (29%) **f. Chocolate** 9 (43%)
g. Cheese 10 (48%) h. Vegetable 5 (24%) i. None of these
j. Don't know 2 (10%)

D2 Which of these drinks are **RICH** in phosphate? Please circle below as many drinks as you wish.

a) Coffee 5 (24%) b) **Ovaltine 6 (29%)** c) Pure Fruit juice 5 (24%)
d) **Milk** 6 (29%) e) Water 0 (0%) f) Tea 4 (19%)
g) Wine 2 (10%) h) Squash 1 (5%) i) None of these 1 (5%)
j) All of these (0%) k) Don't now 5 (24%)

2 patients commented that they did not know because they did not drink those listed

D3 Which of these foods are **LOW** in phosphate? Please circle below as many foods as you wish.

a) **Fruit** 7 (33%) b) **Vegetables** 10 (48%) c) **Pasta** 7 (33%)
d) Cheese 1 (5%) e) Chocolate f) **Crisps** 1 (5%)
g) Yogurt 5 (24%) h) Nuts i) None of these
j) All of these k) Don't know 5 (24%)

D4 Which of these drinks are **LOW** in phosphate?

a) **Tea** 6 (29%) b) **Wine** 1 (5%) c) **Squash** 10 (48%)
d) Milk 2 (10%) e) **Water** 12 (57%) f) **Coffee** 0 (0%)
g) Ovaltine 1 (5%) h) **Pure fruit juices** 6 (29%)
i) None of these j) All of these k) Don't know 6 (29%)

SECTION E: SELF-REPORTED ADHERENCE TO PHOSPHATE BINDER USAGE

E1 On average, when do you take your phosphate binders?

a. 30 minutes before meals b. During your meal 3 (19%)
c. The time varies 1 (6%) d. **10 minutes before meals** 3 (19%)
e. Just after your meal f. Whenever it is convenient
g. **Immediately before meals** 7 (44%) h. 30 minutes after your meal
i. Don't know 2 (12%)

E2 On average, do you take your phosphate binders as prescribed (Please circle one answer only):

a) Always (never miss a dose) 7 (41%)
b) Fairly regularly (sometimes miss a dose) 5 (29%)
c) Occasionally (frequently miss a dose) 3 (18%)
d) Not at all (never take a dose)

f) Don't know 2 (12%)

Evaluation of a Phosphate Management Protocol to Achieve Optimum Serum Phosphate Levels in Hemodialysis Patients

Dawn Yokum, BSc RD, Georgina Glass, BPharm, DipClinPharm, MRPharmS,† Ching Fun Cheung, BPharm, MRPharmS,‡ John Cunningham, DM, FRCP,§ Stanley Fan, MBBChir, MRCP,¶ and Angela M. Madden, PhD, RD#*

Objective: To evaluate the effectiveness of a protocol designed to optimize serum phosphate levels in patients undergoing regular hemodialysis (HD).

Design: Randomized, controlled trial.

Setting: Hemodialysis units at Barts and the London NHS Trust and satellite units.

Patients: Thirty-four clinically stable adults undergoing regular HD with a serum phosphate level >1.8 mmol/L on at least one occasion within 4 months of starting the study.

Intervention: Management of serum phosphate using a specially designed phosphate management protocol during a 4-month study period implemented by a renal dietitian and renal pharmacist compared with standard practice.

Main Outcome Measure: Change in serum phosphate levels in both groups after 4 months.

Results: Patients managed using the phosphate management protocol had a significantly greater reduction in serum phosphate levels compared with patients receiving standard practice (−0.22 ± 0.67 mmol/L vs. +0.19 ± 0.32 mmol/L, $P = 0.03$).

Conclusion: The phosphate management protocol was effective, and its implementation was associated with significantly better serum phosphate control in patients undergoing regular HD.

This article has an online CPE activity available at www.kidney.org/professionals/CRN/ceuMain.cfm

PATIENTS UNDERGOING REGULAR hemodialysis (HD) are at risk of complications associated with elevated serum phosphate levels that increasingly stimulate parathyroid gland production of parathyroid hormone (PTH), and lead to accelerated bone resorption.[1] Hyperphosphatemia and hypercalcemia also increase the calcium-phosphate product, potentiating metastatic calcification in soft tissues.[2] In addition, patients with elevated serum phosphate experience higher mortality, and those with serum phosphate levels >2.1 mmol/L have a significantly increased risk of dying during their first year of treatment.[3]

Standard thrice-weekly HD is unable to remove excess phosphate effectively from the blood,[4] and therefore patients need to restrict their dietary

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intake of foods rich in phosphate, and need to take oral phosphate binders to control both serum phosphate and PTH levels.[5] Traditionally, patients are taught about the importance of both diet and medication at the start of regular HD, and this is reinforced as treatment continues. A number of studies evaluated the efficacy of such teaching.[6–9] Although some patients showed no clinical benefit from such instruction,[7,8] others reported that higher levels of knowledge about diet and medication and education as received from a dietitian were associated with lower serum phosphate levels.[6,9]

Despite these interventions, hyperphosphatemia remains a problem for a substantial number of HD patients,[10] and there is a need to investigate standardized and reproducible protocols to facilitate the management of hyperphosphatemia. To this end, a phosphate management protocol was devised to enable renal dietitians and renal pharmacists to extend their traditional role in this area of practice under the auspices of a Patient Group Direction.[11] The aim of this study was to evaluate the effectiveness of the protocol, designed to optimize serum phosphate levels in patients undergoing regular HD.

Methods

Subjects

Subjects were recruited from adult outpatients with chronic renal failure undergoing regular HD (3 times per week) and attending daytime sessions at Barts and London (BLT) NHS Trust between June and September 2003. Inclusion criteria comprised age >18 years, clinically stable condition, fluency in English, mental alertness, and elevated serum phosphate levels. Patients with malignancy, gastrointestinal disorders including malabsorption, and planned surgery were excluded. Before entry into the study, serum phosphate levels were monitored for 4 months, and patients with at least one value >1.8mmol/L during this period were invited to participate. A total of 34 patients fit the study criteria, agreed to participate, and provided written, informed consent. They were randomized into one of two study groups, using a computer-generated random number list:

(1) Phosphate management protocol (PMP) group; and
(2) Standard practice (SP) group.

At recruitment, the two groups were comparable in terms of age, sex, ethnic group, etiology of kidney disease, length of time since commencing regular HD, and body mass index (BMI) (Table 1). All study patients were reviewed, and their blood results were monitored once a month for the 4-month duration of the study. At each monthly visit, all patients were seen individually by a renal dietitian who devised an individual care plan. Individual dietary advice was given after taking a diet history,[12] and comprised verbal advice supported by either a detailed low-phosphate diet booklet providing a comprehensive list of high-phosphate foods to avoid and suitable alternatives, or a simplified, handwritten diet action plan. The choice of written material was based on each patient's circumstances and perceived ability to understand the instructions given. Patients were advised while they were undergoing dialysis.

Phosphate Management Protocol Group

In the PMP group, phosphate-binder and alfacalcidol (vitamin D analogue) medication was adjusted, using a specially designed phosphate management protocol. This was developed by the multidisciplinary renal research team, which included a renal consultant, a dietitian, and pharmacists. The protocol comprised two algorithms (Fig. 1) that allowed the renal research pharmacists and renal research dietitian, working together, to change patients' medications as specified within the protocol, without the close supervision of a renal consultant. The protocol was approved by the BLT Patient Group Direction Committee.[11] The algorithms were used to inform changes regarding the dose and type of phosphate binder and the dose of alfacalcidol required to improve patients' serum phosphate, calcium, and intact parathyroid hormone (iPTH) levels. Once a month, while patients were undergoing dialysis, the renal research pharmacists explained the changes in their medication, counseled them about when to take them and about adjustments in relation to the size of their meals, and provided a medication card. Once a month, patients were also seen by the renal research dietitian.

Standard Practice Group

In the SP group, a senior doctor within the renal team reviewed the monthly blood results and

Table 1. Demographic, Clinical, and Nutritional Characteristics of 34 Randomized Patients at Recruitment*

	Phosphate Management Protocol Group (n = 17)	Standard Practice Group (n = 17)	*P* Value
Age (y)	51.1 ± 12.7	47.6 ± 14.4	.46
Male:female ratio (n)	11 M:6 F	12 M:5 F	.71
Race (n)			
Black	5	4	
Indo-Asian	1	2	
White	11	10	
Other	0	1	
Etiology (n)			
Glomerulonephritis	5	2	
Diabetes	3	2	
Hypertension	2	3	
Adult polycystic kidneys	1	2	
Pyelonephritis	0	2	
Unknown	2	2	
Other†	4	4	
Length of time on hemodialysis (y)	2.0 (<1 to 10)	2.5 (<1 to 7)	.5
Nutrition			
Height (m)	1.71 ± 0.10	1.66 ± 0.10	.13
Weight (kg)	71.1 ± 15.8	71.7 ± 13.1	.90
BMI (kg/m^2)	24.3 ± 4.8	26.3 ± 5.5	.27

*Values are expressed as mean ± SD, except where indicated.

†Including focal segmental glomerulosclerosis, immunoglobulin A nephropathy, oxalosis, tuberculosis, and Goodpasture's syndrome.

the dose and type of phosphate binder and alfacalcidol during dialysis ward rounds or at an outpatient clinic. Once a month, patients were also seen by a renal dietitian, but were not seen by a pharmacist.

Monitoring

Routine blood samples were taken before dialysis within the first week of every month. Serum was separated and frozen within 1 hour of blood collection. Serum phosphate and calcium concentrations were analyzed using ultraviolet and color photometric tests, respectively,[13,14] and the calcium-phosphate product (Ca × P) was calculated. Serum calcium concentrations were adjusted with reference to serum albumin (corrected calcium [mmol/L] = measured calcium [mmol/L] + ([40 − albumin (g/L)] × 0.02)). Serum iPTH and aluminium concentrations were measured at the beginning and end of the study by an automated chemiluminescent immunoassay and by atomic absorption spectrophotometry, respectively.[15,16] The adequacy of HD was assessed by single-pool Kt/V, calculated at recruitment and at the end of the study.[17] Weight was recorded at the end of each dialysis session and, using previously recorded height, the BMI was calculated.

Statistical Analysis

Power calculations indicated that a sample size of 17 patients in each group was required to detect a 15% reduction in serum phosphate levels (80% power at a significance level of .05), based on data from BLT HD patients in 2000. The distribution of variables was tested for normality, using the Shapiro-Wilks test (SAS version 8.2, 2001, SAS Institute, Inc., Cary, NC).

At baseline, comparisons were made between the two patient groups, using unpaired *t* tests for normally distributed data (most biochemical/nutritional variables, and age), and Mann Whitney U tests for data not normally distributed (iPTH and time on dialysis). The difference between the baseline and postintervention results within each group was compared using paired *t* tests and the Wilcoxon matched-pairs test. The difference between the change from baseline to postintervention in the two groups was evaluated using unpaired *t* tests and Mann Whitney U tests. Categorical data were compared using the chi-square test (male to female ratio) and McNemar's test and Cochran's test for linear trend (number of patients achieving K/DOQI targets[18]) (Systat version 10.2, 2002, Systat Software UK Ltd., Hounslow, UK). The study protocol was approved

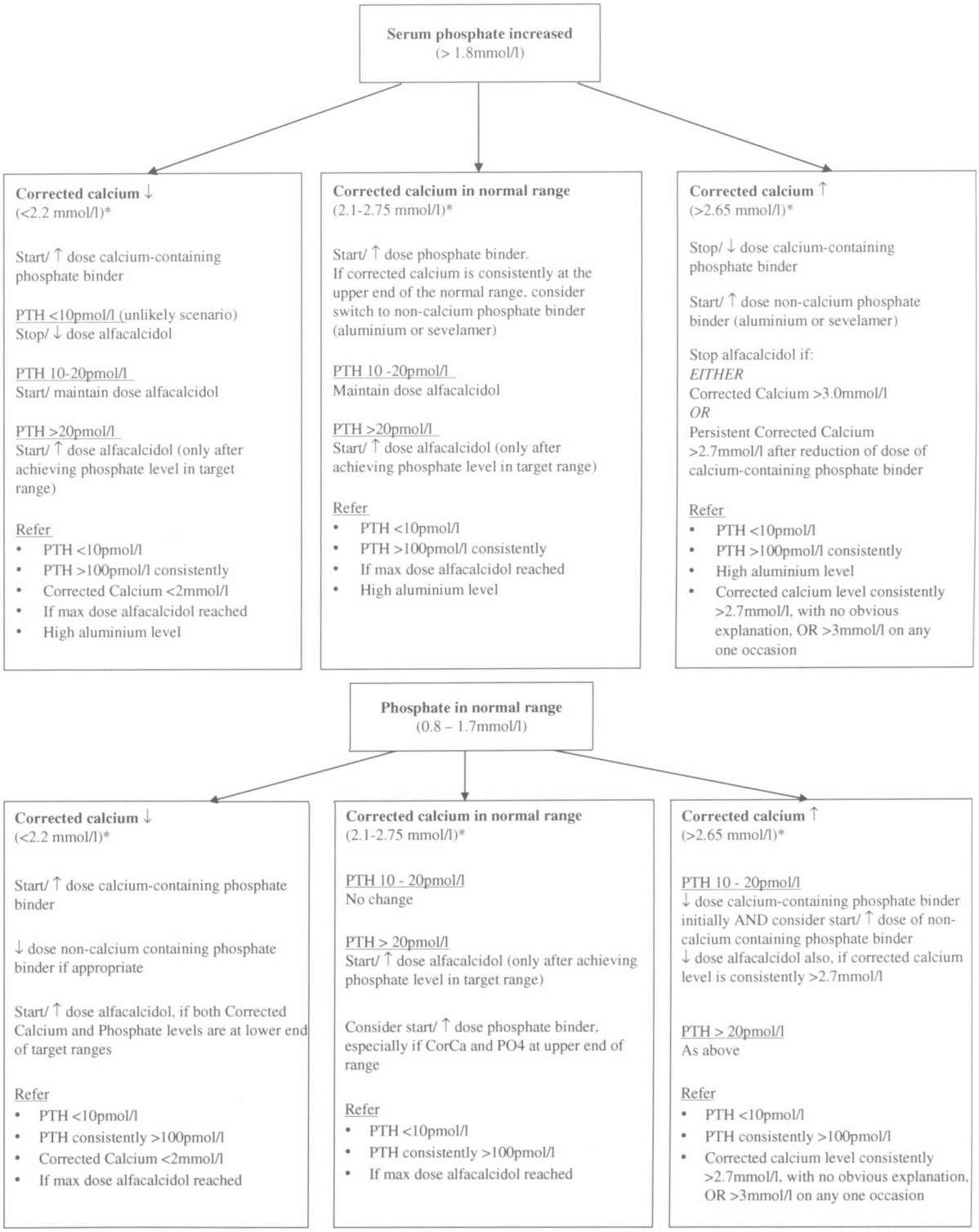

Figure 1. Phosphate management protocol algorithm. *There is a small overlap in the threshold corrected calcium levels of the three treatment pathways, so that patients whose levels fluctuate around these values do not have their medications adjusted at every review. PTH, parathyroid hormone.

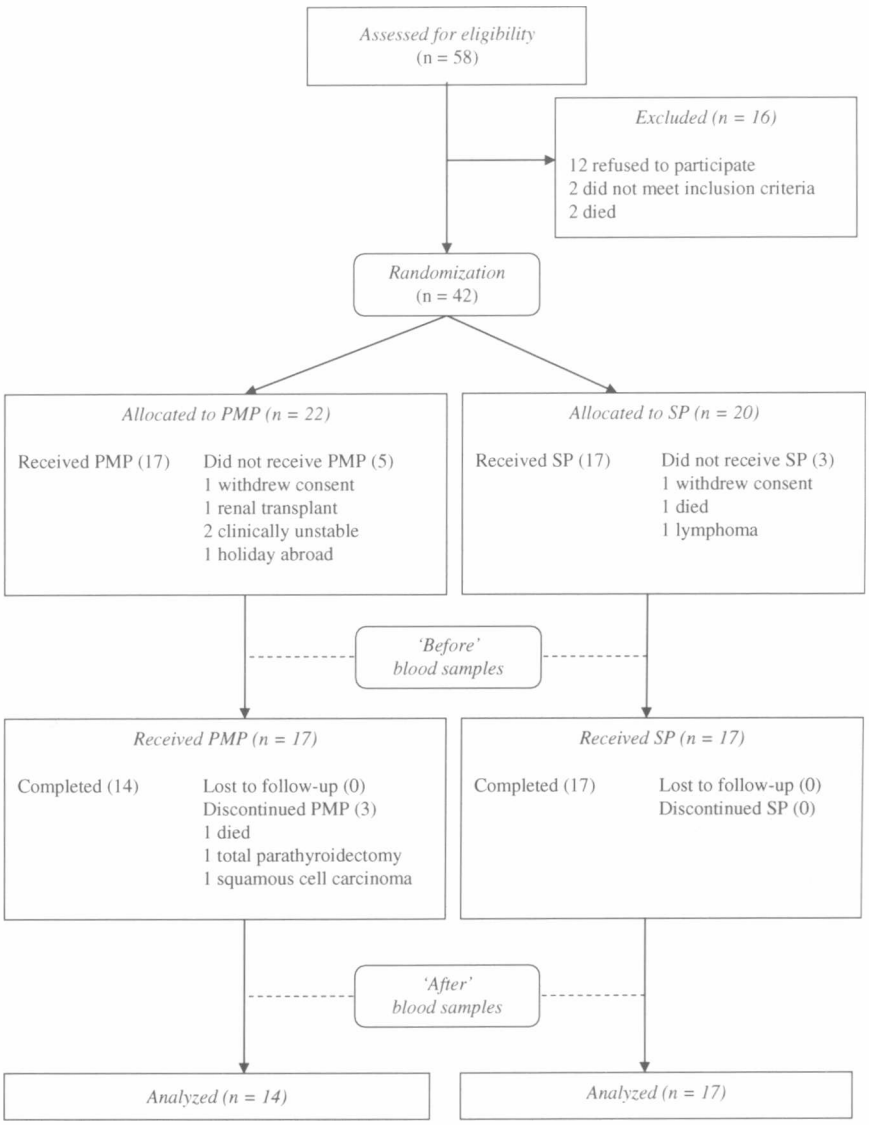

Figure 2. Flow of participants through trial. PMP, phosphate management protocol; SP, standard practice.

by North East London Strategic Health Authority Research Ethics Committee (reference number P/01/092).

Results

Forty-two patients were recruited into the study and were randomized to one of two intervention groups; 34 of these received the interventions (Fig. 2). Three patients did not complete the study, and all of these were allocated to the PMP group. Two were withdrawn in week 6 after developing complicated or confounding medical conditions (total parathyroidectomy for severe hyperparathyroidism, and oropharyngeal squamous-cell carcinoma requiring feeding via gastrostomy), and the third died from septicemia secondary to endocarditis during week 9. Data from these patients were included in the comparative analysis at recruitment (Table 1), but not in subsequent analyses.

Hemodialysis adequacy, as indicated by Kt/V, was comparable between the two groups at recruitment (PMP, 1.30 ± 0.25 vs. SP, 1.32 ± 0.17; $P = .77$) and at the end of the study (PMP, 1.29 ± 0.29 vs. SP, 1.43 ± 0.20; $P = .14$). Only one patient (in the SP group) had an elevated serum aluminium level before the intervention (2.6 μmol/L). This elevation responded to a reduction of her aluminium hydroxide dose. In all other

patients, aluminium levels remained within acceptable limits throughout the study. The BMI remained comparable in both groups throughout the study.

No statistically significant difference was observed in serum phosphate concentrations, corrected calcium, Ca × P, or iPTH between the two groups at the start of the study (Table 2). However, after the study, a significant increase in serum phosphate was observed in the SP group, whereas the PMP group showed a small, insignificant reduction. A comparison between the two groups over the study period showed a significantly greater improvement in serum phosphate levels in the PMP group compared with patients receiving standard practice (-0.22 ± 0.67 mmol/L vs. 0.19 ± 0.32 mmol/L, $P = .03$). Parallel differences in the change in Ca × P product were observed between the two groups, but there were no significant differences in the change in serum corrected calcium or iPTH levels (Table 2).

The proportion of patients achieving the K/DOQI target for serum phosphate increased in the PMP group but decreased in the SP group after the intervention period, but the changes were not significant within groups (Table 3) or between groups (data not shown). Similarly, the proportion of patients meeting multiple K/DOQI targets increased in the PMP group and decreased in the SP group. Again, these trends were not significant (Table 4).

Significantly more changes to the dose of individual phosphate binders were made in the PMP group than in the SP group (median [range] number of dose changes, PMP, 5 [1-7] vs. SP, 0 [0-3]; $P < .001$). The estimated time spent with patients in the PMP group each month by the pharmacists was 19 (range, 8-25) minutes. Patients in the SP group were not seen by the pharmacists.

Eight breaches of the study protocol occurred during the study, relating to physicians changing binders between monthly reviews without reference to the protocol. On each occasion, when the breach was identified by the pharmacist, the blood levels were reviewed promptly against the protocol, and an appropriate amendment was made in compliance with the protocol.

Discussion

The results of this study show that the use of a defined phosphate management protocol can

Table 2. Effect of Phosphate Management Protocol and Standard Practice on Biochemical Variables in Patients Undergoing Regular Hemodialysis*

	Phosphate Management Protocol (n = 14)				Standard Practice (n = 17)					
	Before	After	Change	Intragroup *P* Value	Before	After	Change	Intragroup *P* Value	Intergroup *P* Value Before	Intergroup *P* Value Change
Serum phosphate (mmol/l)	2.03 ± 0.28	1.81 ± 0.54	−0.22± 0.67	0.24	1.88 ± 0.32	2.07 ± 0.25	+0.19± 0.32	.03	.18	.03
Corrected calcium (mmol/l)	2.48 ± 0.26	2.47 ± 0.15	−0.01± 0.28	0.95	2.34 ± 0.26	2.34 ± 0.26	0 ± 0.16	.92	.15	.91
Ca x P ($mmol^2/l^2$)	5.01 ± 0.74	4.43 ± 1.20	−0.58± 1.62	0.20	4.38 ± 0.86	4.80 ± 0.51	+0.41± 0.81	.05	.04	.04
iPTH† (pmol/L)	36 (0.3 to224)	51 (0.3 to175)	−2 (−75 to +40)	0.38	29 (0.3 to 237)	21 (0.3 to 165)	0 (−214 to +26)	.64	.85	.89

*Values are expressed as mean ± 1 SD, except where indicated.
†Median (range).

Table 3. Effect of Phosphate Management Protocol and Standard Practice on Patients Achieving Individual K/DOQI[18] Targets*

K/DOQI Targets for Serum Variables		Number (%) of Patients With Serum Variable Within Target		*P* Value
		Before	After	
PO_4 (1.13-1.80 mmol/L)	PMP (n = 14)	2 (14)	5 (36)	.08
	SP (n = 17)	7 (41)	3 (18)	0.10
Corrected calcium (2.1-2.37 mmol/L)	PMP (n = 14)	5 (36)	4 (29)	.56
	SP (n = 17)	7 (41)	5 (29)	.41
Ca × P product (<4.44 $mmol^2/L^2$)	PMP (n = 14)	3 (21)	7 (50)	.16
	SP (n = 17)	10 (59)	5 (29)	.06
iPTH (16.0-33.0 pmol/L)	PMP (n = 14)	1 (7)	1 (7)	1.00
	SP (n = 17)	2 (12)	4 (24)	.32

PMP, Phosphate management protocol; SP, standard practice: iPTH, intact parathyroid hormone.
*Comparisons were undertaken using McNemar's test.

lead to statistically significantly improved phosphate control over a 4-month period, compared with standard therapy. Although a number of previous studies evaluated the effects of single elements of managing hyperphosphatemia, including dietary counseling and education[6–9,19,20] and pharmacotherapy,[21,22] few have investigated an algorithm-based protocol for the management of hyperphosphatemia. Craven and Moreschi[23] examined the effects of a protocol for administering intravenous calcitriol in HD patients, and concluded that it decreased the incidence of elevated iPTH levels, although no control group was included.

The use of dietary modification and pharmacotherapy is not without risk in this patient population. Dietary phosphate is associated with dietary protein, and over-restriction may compromise nutritional adequacy[24] and lead to undernutrition, with its accompanying risk of increased mortality.[25] No dietary data were collected during this study, so the adequacy of patients' nutritional intake is unknown. However, BMI data suggest that the patients who participated in the study were likely to be well-nourished, and no significant decrease in BMI was observed over the 4-month duration of either arm of the study. Calcium-containing phosphate binders are associated with progressive cardiovascular calcification,[26,27] whereas patients taking those phosphate binders containing aluminum run an increased risk of aluminum toxicity, manifesting as encephalopathy and osteomalacia.[28,29] In the present study, elevated serum aluminum levels were not a concern. Nonabsorbable sevelamer is associated with fewer serious adverse effects, although gastrointestinal symptoms were reported,[30,31] and it is one of the most expensive phosphate binders available.[32] It was speculated that by using a combination of phosphate binders in a systematic manner, the protocol might also reduce the risks associated with individual binders.[22] A large prospective study would be required to address this.

The total staff time required to deliver the phosphate management protocol, compared with the standard treatment, was not measured. Anecdotally, no additional medical staff time was required with the PMP group, but additional pharmacist and dietetic time was required. It could be argued that the additional staff time, rather than the protocol per se, contributed to the improved phosphate control. Future studies are needed to

Table 4. Effect of Phosphate Management Protocol and Standard Practice on Patients Achieving Multiple K/DOQI Targets*[18]

	Number (%) of Patients Achieving K/DOQI						
	Targets Achieved	0	1	2	3	4	*P* Value
Phosphate management protocol (n = 14)	Before	6 (43)	5 (36)	3 (21)	0	0	.18
	After	3 (21)	6 (43)	4 (29)	1 (7)	0	
Standard practice (n = 17)	Before	4 (23)	3 (18)	7 (41)	3 (18)	0	.10
	After	5 (30)	7 (41)	5 (29)	0	0	

*Comparisons were undertaken using Cochran's test for linear trend.

evaluate this and to explore the health-economic implications of the protocol with regard to both staff time and prescribing costs.

The limitations of this study include the small number of patients studied. Although a statistically significant difference in the change of phosphate levels was observed between the two groups, this small change is unlikely to have clinical significance. However, this could be explored in a future study by repeating the study in patients with more poorly controlled serum phosphate rather than in a population with a single serum phosphate level >1.8 mmol/L. It would also be beneficial to measure the residual renal function of patients, which was not performed in the present study, to clarify patients' ability to control their serum phosphate. In future studies, the additional measurement of nutrient intake would allow the effect of dietary advice on phosphate intake to be evaluated directly, and would facilitate the examination of overall nutrient intake adequacy.

This study showed that patients undergoing regular HD had significantly better serum phosphate control while they were being managed with a protocol incorporating patient education, dietary counseling, and pharmacotherapy than did patients receiving standard management. A larger study is required to confirm whether the observed effects can be extended to other dialysis populations.

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