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Hyperphosphataemia in Renal Failure

Causes, Consequences and Current Management

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Abstract

Hyperphosphataemia is prevalent among chronic renal failure and dialysis patients. It is known to stimulate parathyroid hormone and suppress vitamin D3 production, thereby inducing hyperparathyroid bone disease. In addition, it may independently contribute to cardiac causes of death through increased myocardial calcification and enhanced vascular calcification. Hyperphosphataemia is also

associated with cardiac microcirculatory abnormalities. Therefore, phosphate control is of prime importance.

It is important to control phosphate levels early in the course of chronic renal failure in order to avoid and treat secondary hyperparathyroidism, and cardiovascular and soft tissue calcifications. Dietetic restrictions are often difficult to follow long term. Because of its large sphere of hydration and the complex kinetics of phosphate elimination, phosphate is not easily removed by dialysis. Long, slow dialysis may be effective, but this needs logistics and acceptance by patients. Thus, oral phosphate binders are generally required to control serum levels. None of the existing phosphate binding agents is truly satisfactory. Aluminium-containing agents are highly efficient but many clinicians have abandoned their use because of the potential toxicity. Despite of the wide use of calcium-containing agents, there was a link with hypercalcaemia and soft tissue calcifications. Novel phosphate binders in the form of polyallylamine hydrochloride, polyuronic acid derivatives and lanthanum carbonate appear promising. In this review, we discuss causes of hyperphosphataemia, pathological consequences and modalities of treatment.

Elevated serum phosphate is a usual accompaniment of end-stage renal disease (ESRD) and dialysis, in the absence of dietary phosphate restriction or supplemental phosphate binders. The pathological consequences of hyperphosphataemia include the development and progression of secondary hyperparathyroidism, soft tissue calcification and possibly cardiovascular complications. Indeed, poor phosphate control is associated with morbidity and mortality, increased hospitalisation, premature death, reduced quality of life and increased cost of care.[1-3] However, phosphate control has not improved over the past two decades. Several factors are probably responsible for this, including poor compliance with diet and medication, inadequate phosphate clearance by dialysis and the lack of an ideal phosphate binder.

Phosphorus is one of the most abundant constituents of all tissues and is a major component of bone. The total phosphate content in a 70kg man is approximately 700g. About 85% is present in the skeleton, 14% is intracellular and less than 1% is in extracellular fluids. In extracellular fluid, some 10% of phosphate is bound to proteins, and one third is complexed to sodium, calcium and magnesium. Inorganic phosphate is present in the circulation as monohydrogen phosphate, which is divalent, and as dihydrogen phosphate, which is monovalent.[4] The concentration of phosphate in the serum has a wider physiological range than that of calcium and varies with age. It is highest during the neonatal and early childhood periods and declines thereafter. The mechanism for this difference is not established, but may be related to the higher values of circulating growth hormone in growing children than in adults and to the associated increase in tubular reabsorption of phosphate.[5] The average daily intake of phosphate is around 1000–1500mg, which is balanced by faecal and urinary outputs resulting in a phosphate balance of zero. The internal metabolism of phosphate includes digestive juice secretion and reabsorption, and absorption of phosphate occurs maximally at the jejunum. The intestine absorbs 60–70% of dietary phosphate. Normally parathyroid hormone (PTH) maintains phosphorus and calcium balance in the body by:

- stimulating the kidneys to reabsorb or to excrete these minerals, if necessary, or by
- acting to release calcium and phosphorus from bone.

Complex interactions between vitamin D, PTH and other hormones, and cations and other dietary components as well as certain medications, allow the body to maintain mineral homeostasis and nor-

mal bone turnover.[6] Serum phosphate levels are kept normally in the range of 0.8–1.4 mmol/L and serum total calcium levels in the range of 2.12–2.62 mmol/L.

1. Renal Handling of Phosphate

As much as 50% of the filtered load of phosphate is reabsorbed in the first third of the proximal tubule. Within this segment only 10% of sodium and water is reabsorbed. In the last two thirds of the proximal tubule 20% of the filtered load of phosphate is reabsorbed and in this segment a parallel percentage of water and sodium is also reabsorbed. There is no evidence to suggest any transport of phosphate within the loop of Henle. In the distal convoluted tubule, 5–10% of the filtered load of phosphate is reabsorbed under basal conditions in animals that have undergone parathyroidectomy. This segment is responsive to PTH as are all other segments except the loop of Henle and the collecting duct.[7] The administration of PTH results in a lowering of the tubular reabsorption of phosphate by as much as one half and a lowering of the distal tubular reabsorption from 5–10%. In the collecting duct, up to 3% of the filtered load of phosphate is reabsorbed. However, this can be increased to 10% in the presence of an increased luminal phosphate concentration or increased flow rates.[8]

Renal impairment is associated with elevated PTH levels, and the hypersecretion of PTH is initially appropriate because PTH can correct both the hypocalcaemia and the hyperphosphataemia. The effect on renal phosphate handling is manifested by a progressive reduction in the fraction of the filtered phosphate that is reabsorbed, from the normal value of 80–95% to as low as 15% in advanced renal failure. As a result, phosphate balance and a normal plasma phosphate level are generally maintained (at the price of hyperparathyroidism) until the glomerular filtration rate (GFR) falls below 25–30 ml/min.[9,10]

2. Causes of Hyperphosphataemia

Whereas the input of phosphate to the circulation may be from a host of exogenous or endogenous sources, the major underlying cause of phosphate retention and hyperphosphataemia is impaired renal phosphate excretion. The degree of hyperphosphataemia is a function of the difference between the rate of entry of phosphate and the renal excretion of phosphate. If renal function is normal, clinically significant hyperphosphataemia seldom develops, unless an event such as massive tissue breakdown occurs and leads to the development of renal failure.[11]

The various mechanisms and causes for the development of hyperphosphataemia are summarised in table I.

Table I. Mechanisms and causes for the development of hyperphosphataemia

I. Decreased glomerular filtration rate
Acute and chronic renal failure
II. Increased tubular reabsorption of phosphate
Parathyroid dysfunction: hypoparathyroidism; pseudohypoparathyroidism; transient parathyroid resistance of infancy
Endocrine dysfunction: hyperthyroidism; tumoral calcinosis; growth hormone excess; juvenile hypogonadism; postmenopausal state
High ambient temperature
Bisphosphonates
III. Increased phosphate loads
Exogenous loads: enemas and laxatives; vitamin D intoxication; parenteral phosphate; blood transfusion; white phosphorus burns
Endogenous loads: cellular shift in diabetic ketoacidosis; lactic acidosis; tissue hypoxia; rhabdomyolysis; cytotoxic therapy of neoplasms; haemolysis; malignant hyperthermia
IV. Miscellaneous
Familial intermittent hyperphosphataemia

3. Pathophysiological Consequences of Hyperphosphataemia

3.1 Secondary Hyperparathyroidism

Hyperphosphataemia exerts a direct stimulatory effect on PTH secretion and parathyroid cell proliferation, both *in vitro* and *in vivo*. Parathyroid overactivity in renal failure was explained by the tradeoff hypothesis of Bricker et al.[12] Hyperphosphataemia is thought to reduce the blood levels of ionised calcium, which in turn stimulates PTH secretion. The high levels of PTH reduce tubular reabsorption of phosphorus, cause phosphaturia, and return both serum phosphorus and calcium toward normal, but at the expense of higher circulating PTH levels. However, more recent work has cast doubt on this with the observation that hyperparathyroidism can occur even in the presence of high serum calcium and that hyperphosphataemia also stimulates PTH secretion independent of serum calcium concentration.[13] Furthermore, phosphate retention will result in inhibition of the activity of the renal enzyme 1α-hydroxylase that is responsible for the conversion of 25(OH) vitamin D3 to its metabolite 1,25(OH) 2 vitamin D3. Phosphate retention can also inhibit the calcaemic response to PTH. It has been observed that hyperphosphataemia exacerbates secondary hyperparathyroidism in dialysis patients despite their receiving calcitriol treatment.[14] These results suggested an effect of a low phosphorus diet in controlling PTH secretion.

A direct effect of phosphorus on PTH secretion and parathyroid cell proliferation has been noted both *in vitro* and *in vivo*. Thus, a post-transcriptional decrease in PTH mRNA levels in rats fed a low phosphorus diet was observed.[15] Also, in rats with experimental renal failure, a high phosphorus diet increased parathyroid cell proliferation, whereas a low phosphorus diet had the opposite effect. Moreover, a moderate phosphorus restriction decreased PTH mRNA expression in rats with mild renal failure. It has been recently shown *in vitro* that hyperphosphataemia correlates with decreased binding of parathyroid cytosolic proteins to the PTH mRNA 3 untranslated regions, which determine a decrease in mRNA stability.[16] Moreover, it seems that hyperphosphataemia can alter the sensitivity of parathyroid glands to extracellular ionised calcium. Thus, studies *in vitro* have shown a rightward shift in the PTH-Ca^{2+} curve, which renders parathyroid cells less sensitive to inhibition by ionised calcium.[17] These results would suggest that phosphorus might interfere with the intracellular signalling pathway.[18-25]

3.2 Soft Tissue Calcification

Uraemic extra-skeletal calcification can affect arterial walls (vascular calcification), organs such as the heart, lungs and kidneys (visceral calcification), and periarticular, cutaneous and subcutaneous tissues.

Factors that may promote this calcification include elevated levels of PTH, tissue alkalinity, hyperphosphataemia and, in particular, elevated calcium-phosphate (Ca×P) product.[26]

3.3 Calciphylaxis

The first description of calciphylaxis occurred in the late 1960s and early 1970s.[27] The syndrome is characterised by cutaneous eruptions usually occurring in patients on dialysis or after renal transplantation. The skin lesions often present as areas of painful mottling resembling livedo reticularis with superficial violaceous nodules involving the tips of the toes or fingers or occurring about the ankles, thighs or buttocks. As the lesions progress, they become haemorrhagic with ischaemic dry necrosis. The bilaterally symmetric, superficial nature of these lesions and persistence of palpable pulses distal to the necrosis are characteristic findings.[28]

In some patients, control of hyperphosphataemia resulted in a dramatic improvement of this syndrome. Special emphasis should be placed on rapid control of parathyroid hormone and hyperphosphataemia, and the use of a normal or low dialysate calcium concentrations.[29] The use of calcium containing phosphate binders should be avoided since the ingestion of large amount of calcium has been associated with calciphylaxis.[30] Non-calcaemic phosphate binders such as sevelamer hydrochloride

(sevelamer) or the more recently described lanthanum carbonate may be helpful in the prevention and management of this condition in the future.

3.4 Interference with Calcitriol

A common cause of failure of calcitriol therapy to decrease PTH levels is the presence of hyperphosphataemia. The mechanism is not clear but it appears that hyperphosphataemia has a direct action on increasing parathyroid gland size.[31] In addition, it has been shown that as gland size increases, vitamin D receptor (VDR) expression on the cell surface decreases. Thus, hyperphosphataemia may decrease VDR expression via an increase in gland size. An alternative explanation is a direct action of hyperphosphataemia at the VDR site, with phosphorus inducing a resistant state by interfering with calcitriol binding to the receptor.[32-35] Original earlier data by Korkor et al. and Dusso et al. showed that in advanced renal failure the binding of calcitriol to VDR was decreased by the magnitude of the severity of the hyperphosphataemia.[36-38] Hypothetically it is also possible that hyperphosphataemia may interfere with the calcium sensor receptor at the membrane site of the parathyroids.[39]

3.5 Cardiovascular Complications

Nearly half the deaths of dialysis patients are due to cardiovascular disease.[40] Hyperphosphataemia is prevalent in dialysis patients and serum phosphate levels often exceed 2 mmol/L. An association exists between hyperphosphataemia, elevated Ca×P product and vascular calcification.[1,41,42] Certainly, hyperphosphataemia induces smooth muscle cell mineralisation *in vitro*, although the mechanism is not yet known. One proposed pathway way is outlined below:[43]

- increased osteogenic gene expression, including core-binding factor-1 (cbfa-1) and downstream targets osteopontin and osteocalcin
- decreased smooth muscle specific gene expression
- stimulation of secretion of potential mineral nucleating molecules such as matrix vesicles, alkaline phosphatase, calcium binding proteins and collagen-rich extracellular matrix.

Recently, the transcription factor core-binding factor-1 was found to be a major regulator of osteocalcin, osteopontin and type I collagen gene expression, and to be absolutely required for osteoblast differentiation.

Hyperphosphataemia independently increases cardiovascular mortality and morbidity. The potential mechanisms through which hyperphosphataemia may contribute to this are manifold. It was speculated that elevated phosphorous might aggravate the effects of coronary atherosclerosis through increased vascular calcification and smooth muscle proliferation.[44] It has also been suggested that the vascular calcification may alter microcirculatory haemodynamics through increased extra vascular resistance and further compromise myocardial perfusion.[45]

3.5.1 Cardiac Tissue Calcification

Calcification of cardiac tissue has been reported in nearly 60% of dialysis patients at autopsy.[46,47] These deposits have been identified in the myocardium, pericardium, conduction system, aortic and mitral valves, small myocardial arteries and coronary arteries. Damage to normal cardiac tissues following calcification may lead to abnormal conduction and arrhythmia, left ventricular dysfunction, aortic and mitral stenosis and regurgitation, and complete heart block. Hyperphosphataemia plays a fundamental role in the pathogenesis of ischaemic plaques, which are highly sensitive indicators of coronary atherosclerosis.[48]

Arterial stiffness is another important factor in increasing mortality and morbidity. In patients with ESRD, the arterial stiffness is increased compared with age and blood pressure matched non-uraemic controls.[49,50] However, this modification affects elastic and muscular type arteries independently of the presence of atherosclerotic plaques.[51,52]

Autopsy studies[53] and clinical observations using electron-beam computed tomography (CT)[54] showed a high prevalence of rapidly progressing calcified coronary plaques in uraemic patients.

Haemodialysis patients were found to have a much higher prevalence of cardiac valve calcification by echocardiography than age- and gender-matched controls. Calcification of the mitral annulus was seen in 44.5% of dialysis patients compared with 10% of healthy individuals, and calcification of aortic annulus was noted in 52% of dialysis patients compared with 4.3% of controls.[47,55]

Cardiac tissue previously damaged by infarction, age-related degeneration or long-term arterial hypertension may be particularly susceptible to metastatic calcification in the milieu of elevated serum phosphate levels and Ca×P products.[56] Thus, patients with poor long-term phosphate control and existing cardiac damage may be at greater risk for calcific heart disease and cardiac death due to metastatic calcification. Another factor to be considered in the aetiology of myocardial calcification is the calcium side of the Ca×P product. Therefore, the use of calcium-free (and aluminium-free) phosphate binders such as sevelamer or lanthanum carbonate for the management of ESRD patients with hyperphosphataemia at risk of calcific cardiac disease seem particularly appealing since calcium loading is avoided.

3.5.2 Atherosclerosis and Dyslipidaemia

Low calcium, high phosphate and PTH levels are reported to have independent impacts on arterial wall compliance and thickening.[57] Some of these changes are shown to suppress lipoprotein-regulating enzymes, including hepatic triglyceride lipase (HTGL), lecithin:cholesterol acyltransferase (LCAT) and lipoprotein lipase (LPL), resulting in an adverse lipid profile with increased intermediate-density lipoprotein and decreased high-density lipoprotein levels. These changes are independently associated with arterial wall sclerosis in uraemia.[58] Deranged homeostasis of calcium, phosphate and PTH has significant influence on these factors.

3.6 Effects on Other Organs

Numerous studies have shown that uraemic hyperphosphataemia and secondary hyperparathyroidism may also affect the function of a number of other organs and tissues besides the bone and kidney, including the brain, heart, smooth muscles, lungs, erythrocytes, lymphocytes, pancreas, adrenal glands and testes. These effects might be mediated via the widespread distribution of the classical PTH/PTH-related peptide (PTHrP) receptors and via the novel PTH_2 receptors. Table II demonstrates these effects.[59]

3.7 Others

By analysing data from two large US Renal Data System (USRDS) national studies, Ganesh et al. found that the case mix adequacy study (CMAS) and the Dialysis Morbidity and Mortality Study (DMMS) waves 1, 3 and 4, a 20% greater risk of death resulting from infection and unknown causes among patients with substantial hyperphosphataemia.[60] It is not clear how serum phosphate levels may be related to infection-related death. It is conceivable that hyperphosphataemia may impair immune system function or induce poor wound healing arising from abnormalities in the microcirculation.

4. Clinical Associations of Hyperphosphataemia

Hyperphosphataemia is a major trigger for the onset of hyperparathyroidism in patients with chronic renal failure, which may result in bone pain, pathological fractures, proximal myopathy and growth retardation in children.[61] In addition, it contributes to the anaemia of renal failure,[62] and it has been suggested that hyperphosphataemia accelerates the progression of chronic renal failure by precipitation of calcium phosphate in renal tubules or interstitium, or by inducing glomerular hypertension.[63]

Uraemic pruritus that can be attributed to hyperphosphataemia and hyperparathyroidism is one of the most frustrating, common and potentially disabling symptoms in patients with ESRD. It is often generalised but may be particularly prominent over the posterior chest wall.[64]

The Ca×P product is now regarded by many nephrologists as the major determinant of the progression and regression of metastatic calcium deposits, and the value of 70 in mass units or 5.6 in SI

Table II. The effects of phosphate on non-classical target organs

Organ	Acute response	Chronic response
Nervous system	EEG changes, peripheral neuropathy, abnormal metabolism of phospholipids and neurotransmitters	Neurobehavioural disturbances, EEG changes, peripheral neuropathy, abnormal metabolism of phospholipids and neurotransmitters
Pituitary gland	↑ Secretion of prolactin	↑ Secretion of prolactin
Adrenal cortex	↑ Aldosterone secretion	↓ Aldosterone secretion
β Islets of pancreas	Stimulation of insulin secretion	Glucose intolerance, impaired insulin secretion
Testes	↓ Serum testosterone	↓ Serum testosterone
Heart	↑ Inotropic and chronotropic responses, ↑ coronary perfusion	Abnormal energy metabolism, ↓ cardiac output
Vascular system	Vasodilatation	
Skeletal muscles	↑ Proteolysis	↑ Proteolysis, abnormal energy metabolism
T lymphocytes	Stimulation of mitogen-induced proliferation and cytokine secretory response	↓ Mitogen-induced proliferation and cytokine secretory response
B lymphocytes	↓ Mitogen-induced proliferation and antigen-stimulated Ig production	↓ Mitogen-induced proliferation and antigen-stimulated Ig production
PMNLs	Stimulation of random migration	↓ Chemotaxis, random migration, phagocytosis and bactericidal activity
Erythrocytes	↓ Erythropoiesis, ↑ osmotic fragility	↓ Survival of erythrocytes
Lungs		Microcalcifications, ↓ pulmonary diffusing capacity, ↑ RV pressure and hypertrophy
Lipid metabolism	↑ Lipolytic activity in plasma	↓ Lipolytic activity in plasma, ↑ plasma triglyceride levels, impairment of fatty acid oxidation in skeletal muscles and myocardium
Skin		Microcalcifications, pruritus, necrosis of the skin (rare)

EEG = electroencephalogram; **Ig** = immunogloublin; **PMNL** = polymorphonuclear lymphocytes; **RV** = right ventricular; ↑ indicates increased; ↓ indicates decreased.

units has been suggested as the threshold above which metastatic calcification occurs.[1,56] These calcifications are widespread in chronic renal failure and affect peri-articular sites, large and small arteries, cornea and conjunctiva, lung, myocardium and heart valves, kidney, gastric mucosa and subcutaneous tissues.

Large calcium phosphate deposits around joints can limit mobility. Calcification of the myocardium can cause reduction in left ventricular function and may cause arrhythmias. Calcific aortic stenosis causes the usual features of that disease and has proved fatal. Large vessel calcification is often particularly prominent in patients with diabetes mellitus, and progressive calcification of small and medium vessels can cause digital gangrene, particularly in the limb bearing a shunt or fistula.[65]

5. Why Should We Treat Hyperphosphataemia?

Poor phosphate control correlates significantly with morbidity and mortality among patients with ESRD and dialysis patients. Increased hospitalisation, premature death, reduced quality of life and increased cost of care have been reported.[66]

Data obtained from the USRDS, the CMAS and the DMMS wave 1 found that those patients with serum phosphorus levels >6.5 mg/dl had a 27% higher mortality risk (RR = 1.27) than patients with phosphorus level of 2.4–6.5 mg/dl.[41] Furthermore Block et al. found that a Ca×P product >72 mg^2/dl^2 was associated with a significantly higher relative risk of death (RR = 1.34).[1,42] These results correlate well with previously published data suggesting an increased risk of metastatic calcification at levels above 60–75 mg^2/dl^2.

Arterial calcification has recently been associated with elevated Ca×P product, and dialysis patients

have been shown to have 2.5–5 times higher coronary artery calcification scores than non-dialysis patients, using electron beam CT.[67] This technique has been shown to have a high sensitivity (84%) for predicting coronary disease in the general population and the calcification score correlates with luminal stenoses. However, it is known that in dialysis patients the calcification is often within the arterial wall and may not be contributing to luminal stenosis so that extrapolation of risk may not be valid in this group of patients. However, Block et al. surprised the nephrology community with the finding that hyperphosphataemia is associated with reduced survival and most of the excess deaths were from cardiac causes.[1,41,42] The magnitude of the risk is illustrated by the fact that hyperphosphataemic compared with normophosphataemic patients have a 52% higher risk of death from coronary artery disease, a 26% higher risk of sudden death, a 34% higher risk from other cardiac causes and a 39% higher risk of death from cerebrovascular accidents.[68] It is tempting to suggest that the excess cardiac deaths are directly related to higher calcification scores derived from CT studies but this remains unproven.[69] Further prospective studies are required to confirm this.

6. Where Are We Now?

Block et al. found that 50% of haemodialysis patients have a serum phosphate level >6.0 mg/dl and 25% of patients have a level >7.4 mg/dl.[1] These results were similar to those published by Lowrie and Lew for over 17 000 patients receiving haemodialysis in 1988. Indeed, their analysis also showed that 25% of patients had a phosphate level >7.2 mg/dl.[2] This comparison concludes that the ability to control serum phosphate level has changed very little between 1988 and 1993. Several factors could be responsible for this. Firstly, poor compliance with both diet and medication use is common among patients with ESRD. Secondly, phosphate clearance by dialysis itself has not improved over the past two decades, and thirdly is the lack of an ideal phosphate binder. There was no target given in the Dialysis Outcomes Quality Initiative (DOQI) recommendations for appropriate phosphate levels.[64] The British Renal Association Standards document recommends a target range for serum phosphate of 1.2–1.7 mmol/L for HD and 1.1–1.6 mmol/L for PD. The UK Renal Association Registry now has serial data on phosphate control and it is evident that most centres have difficulty in achieving the suggested standards. Even the best performing centre had <50% of haemodialysis patients within the target range. Overall, for England and Wales only one third of haemodialysis patients have control of serum phosphate within the suggested standard range. There is some evidence of an improvement over recent years in peritoneal dialysis patients but not for haemodialysis patients (figures 1 to 3).[70]

7. Treatment of Hyperphosphataemia

Given that hyperphosphataemia continues to affect more than half of the dialysis population, its prevention and treatment are one of the major goals of management of chronic renal failure. The main methods of achieving control are reduction of dietary intake, reduction of gastrointestinal absorption by use of binding agents and removal by dialysis.

7.1 Dietary Intervention

The major sources of dietary phosphate include meat, fish, dairy products, certain vegetables and soft drinks. Processed foods usually contain significantly more phosphate than natural products. The usual Western diet contains 800–2000 mg/day (26–67 mmol/day) of phosphate depending mainly on the protein content.[71] Decreasing dietary phosphate is very difficult to achieve without significant reduction in protein intake, which may put patients with renal failure at risk of malnutrition.[72]

Phosphate rich foods include milk and cheese, egg, all meat, particularly liver, kidney and veal, fish, particularly fatty fish such as salmon, trout, sardines, shellfish and crustacea, peas, beans, lentils and soya products, bran and all bran containing cereals, and other coarse grain foods such as oatcakes.

In patients on maintenance dialysis, who are usually catabolic, a diet containing 1.0–1.2 g/kg/day

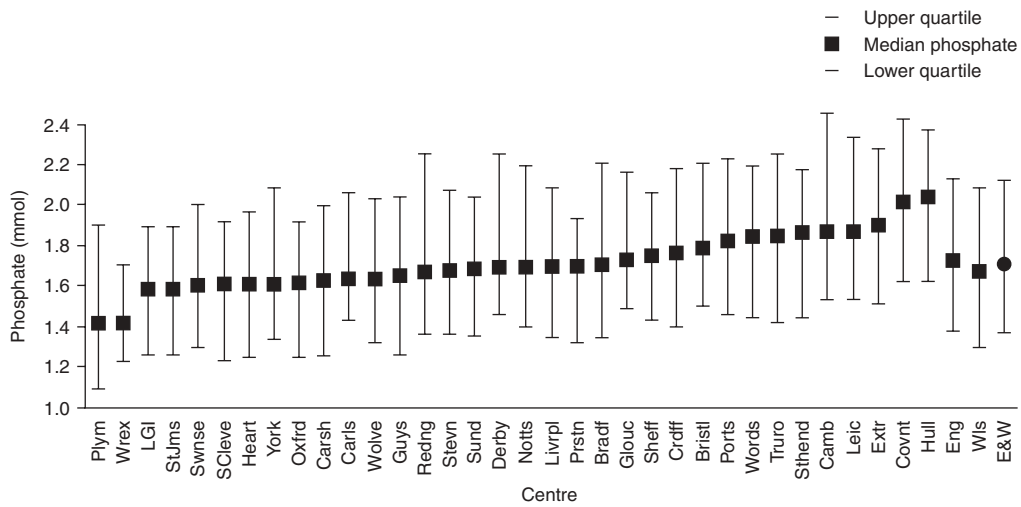

Fig. 1. Current phosphate control levels in patients on haemodialysis from ten UK centres (1997–1998). Graph indicates the percentage of patients with a serum phosphate level between 1.2–1.7 mmol/L as recommended by the British Renal Association Standards.

protein is needed to achieve neutral nitrogen balance. However, such a diet contains approximately 800–1200mg (20–40 mmol) of phosphate. As the intestinal absorption ranges between 40–80% of the ingested phosphate, the amount of absorbed phosphate varies between 10–30 mmol/day and 70–210 mmol/week. Usually this cannot be matched by the decreasing phosphate excretion of the failing kidneys or by the dialytic phosphate removal in patients on maintenance dialysis.[73]

7.2 Dialytic Phosphate Removal

Although phosphate removal by dialysis would seem the appropriate method to control hyperphos-

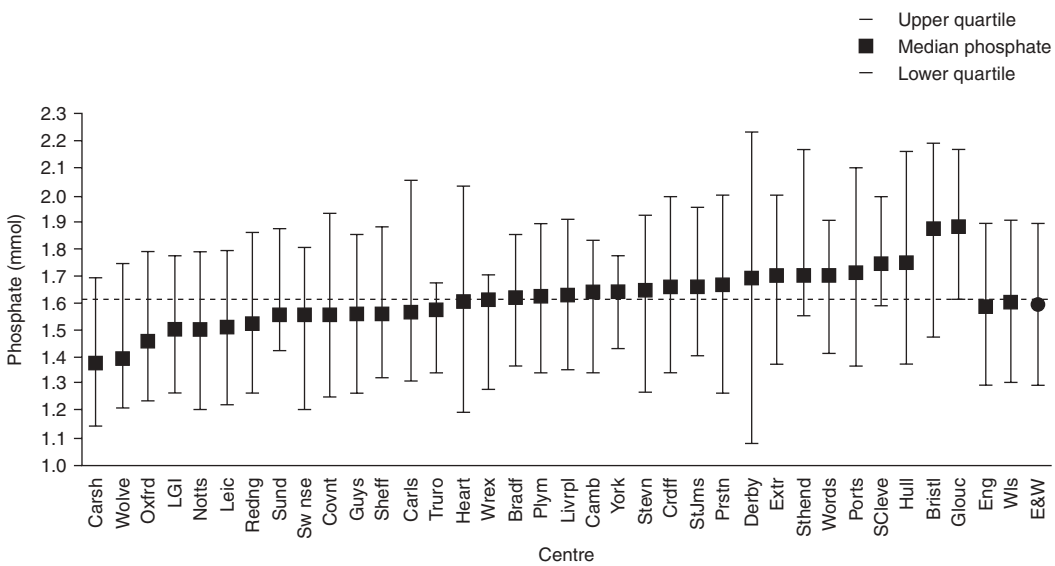

Fig. 2. Current phosphate control levels in patients on peritoneal dialysis from ten UK centres (1997–1998) [n = 2756]. Graph indicates the percentage of patients with serum phosphate levels between 1.1–1.6 mmol/L as recommended by the British Renal Association Standards.

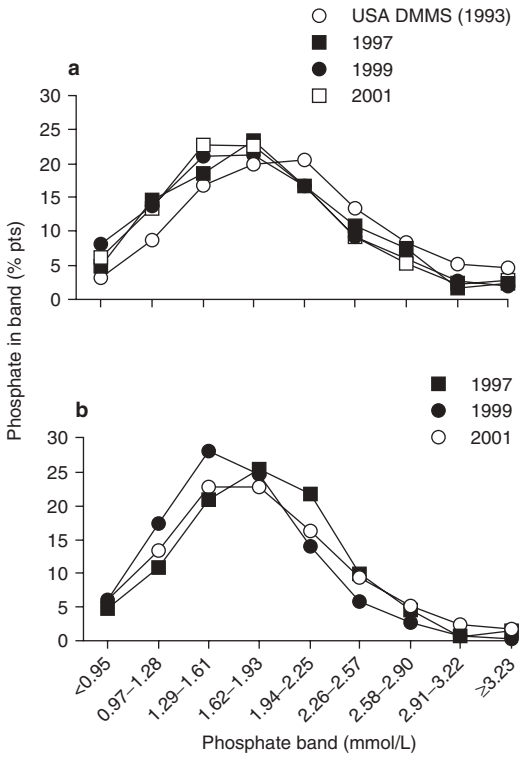

Fig. 3. Control of serum phosphate levels from 1993–2001. Serum phosphate level distributions in patients on haemodialysis (**a**) and peritoneal dialysis (**b**) from the UK Renal Registry Report 2002 and the Dialysis Morbidity and Mortality Study (DMMS).

phataemia, the various available dialysis techniques can not easily achieve this goal. Thus, about 90% of dialysis patients need further therapeutic manoeuvres to control hyperphosphataemia.

There is no currently used intermittent extracorporeal or peritoneal dialysis system able to remove all the phosphorus contained in a normal diet. On average only 500–1000mg of phosphate is eliminated by one dialysis treatment. The best results are obtained with the use of large surface area dialysers with prolonged dialysis times and high blood flow rates. In peritoneal dialysis, the weekly removal of phosphate has been estimated to be around 2200mg, but depends on the distribution of isotonic and hypertonic peritoneal dialysis fluids.[74] Because continuous ambulatory peritoneal dialysis (CAPD) is a continuous daily treatment the net weekly removal of phosphate is around 10% greater than in haemodialysis (table III). This may explain the observation that serum phosphate is easier to control during CAPD.[75]

Haemofiltration or haemodialfiltration seem to be somewhat more effective than conventional haemodialysis, again because of the continuous nature of these treatments.[76,77] Kinetic studies of haemodialysis have shown that serum phosphate levels drop rapidly in the first 1–2 hours of treatment and then reach a plateau. The amount of phosphate removed decreases significantly in the second half of dialysis. Serum phosphate levels then rise relatively quickly in the first few hours after termination of dialysis - the so-called 'rebound phenomenon'.[78]

Dialysis has a limited ability to remove phosphate. Despite of the fact that dialysis membranes are relatively efficient, there is only a small efflux of phosphate from the large intracellular stores into the extracellular fluid, which is undergoing dialysis. Probably, lengthening dialysis or using larger higher efficiency dialysers might enhance phosphate removal, but this is often limited by logistics and poor acceptance by patients. The much greater efficacy of longer haemodialysis sessions, such as 8 hours three times weekly has been convincingly demonstrated by the Tassin Centre, Paris, France, experience where they achieved normal serum phosphate levels in the absence of any oral phosphate binding therapy.[79] Similar good results were reported by Kooistra and colleagues in the Netherlands in their proposed short haemodialysis schedule.[80] While it appears to Farrington and coworkers that frequency of dialysis may be a more significant factor than duration alone, as they found that serum phosphate levels are higher after long dialysis than short dialysis despite of the removal of significant phosphate mass.[81] Indeed, the results were most marked in the nocturnal haemodialysis schedule. In a crossover

Table III. Phosphate removal by dialysis

Phosphorus:
is mostly found intracellularly
has a large sphere of hydration
is cleared rapidly from serum in first 2 hours of haemodialysis
levels rebound significantly at 3–4 hours post-haemodialysis
Consequently slightly better clearance by peritoneal dialysis

study, the serum phosphate levels of eight chronic dialysis patients were measured during 5 months of conventional haemodialysis and then after the switch to 5 months of daily nocturnal 8–10-hour haemodialysis. Serum phosphate levels were considerably lower with nocturnal haemodialysis (1.3 vs 2.1 mmol/L, $p < 0.001$). Furthermore, nocturnal haemodialysis patients increased their dietary phosphate intake by 50% and did not require phosphate binders after the fourth month.[82]

7.3 Reduced Calcium Dialysate

The importance of a significant gradient of calcium as a factor in soft tissue calcification is demonstrated by the observation of Fernandez and Montoliu.[83] A marked negative gradient between dialysate calcium and plasma induced the progressive disappearance of extraskeletal calcifications. Furthermore, reduction of the dialysis fluid calcium concentration has been shown to reduce hypercalcaemia in haemodialysis patients without deleterious effects on bone histology.[84] Cunningham, Piraino and Hutchison demonstrated these effects in CAPD patients using fluid with a calcium concentration of 1.25 mmol/L.[85-87] Use of a low calcium dialysate has the additional advantage of allowing the ingestion of larger doses of calcium, leading to more efficient phosphate binding. Indeed, patient compliance is essential, because reducing calcium dialysate can lead to hypocalcaemia and worse hyperparathyroidism if the calcium supplements are not taken.[88] However, extended treatment with low calcium dialysate may be associated with an increased risk of severe hyperparathyroidism.[89]

7.4 Oral Phosphate Binding Agents

An ideal oral phosphate binder would have a high affinity for binding phosphorus rapidly with low solubility and no systemic absorption. In addition, it should be non-toxic, in a solid oral dose form and palatable, thus encouraging compliance. Although a wide range of oral phosphate binders exist (table IV), none of them fully satisfy these criteria (table V).[90]

Table IV. Existing oral phosphate binders

Aluminium carbonate and hydroxide
Calcium carbonate and acetate
Magnesium carbonate and hydroxide
Calcium ketoglutarate
Calcium alginate
Sodium ferrous citrate
Zirconyl chloride
Polyallamine hydrochloride (sevelamer)
Lanthanum carbonate

Because it is difficult to achieve adequate restriction of dietary phosphate, particularly in dialysis patients whose dietary protein intake is appropriate, phosphate binders are required by most patients with ESRD and patients whose GFR is less than 20–25%. In general, current phosphate binders are more effective when phosphate intake is <1 g/day. When intake increases >1.5 g/day, their effect decreases markedly. Binders must be taken at meal times to maximise their efficacy. The dose of a binder should be commensurate to the meal size and individualised for each patient's serum phosphate level.[91]

7.4.1 Calcium-Containing Phosphate Binders

Calcium Carbonate and Calcium Acetate

The dose of calcium-containing binders should be increased gradually until serum phosphate is controlled or adverse effects appear. Hypercalcaemia is the most common problem, but gastrointestinal symptoms such as change in bowel habit, vague abdominal discomfort and dyspepsia are often reported. Hypercalcaemia has occurred in a substantial percentage of patients who take calcium-containing binders and often it is severe enough to require withdrawal of the binder.

Table V. Characteristics of an ideal phosphate binder

High affinity for binding phosphorus
Low dose required
Rapid phosphate binding
Low solubility
Low systemic absorption (preferably none)
Non toxic
Solid oral dose form
Palatable – encourages compliance

Many studies have demonstrated that both calcium carbonate and calcium acetate are effective in treating hyperphosphataemia in dialysis patients.[92-94]

Several investigators found that calcium acetate is capable of binding intestinal phosphate more effectively per mmol of administered elemental calcium than calcium carbonate.[94-96] Theoretically 1g of elemental calcium as the carbonate would bind 43mg of phosphate, whereas 1g of calcium acetate would bind 106mg. However, compliance and patient tolerability are generally poorer with calcium acetate and the studies showing mean serum phosphate level was reduced more effectively compared with the same dose of calcium carbonate were short-term.

Sheikh et al. demonstrated that calcium carbonate bound phosphate best in an acid environment (pH approximately 5) and the binding capacity is reduced in the neutral pH range.[96] Calcium acetate dissolves more easily at a high gastric pH. Thus, Janssen et al. found that both the acetate and carbonate are equivalent in their binding capacity provided that calcium carbonate is taken on an empty stomach a few minutes before meals.[97] Although the daily intake of calcium was almost halved in patients who took calcium acetate, the number of hypercalcaemic episodes were comparable. Similar results were reported in paediatric and adolescent haemodialysis patients.[98]

Capsules or tablets are probably less effective than liquid suspension, although patient compliance is generally better with capsules than with liquid forms. Comparing generic forms of the same binder demonstrates that some generic preparations of calcium carbonate have been relatively insoluble and subsequently ineffective.[99] Patients with chronic renal failure or on dialysis may have either hypochlorhydria or be taking H_2 receptor antagonists or proton pump inhibitors. These factors may limit calcium carbonate efficacy by raising gastric pH. Calcium acetate is soluble in both acid and alkaline media, and its solubility is less pH dependent.

In addition to calcium carbonate and acetate, other calcium-based phosphate binders are available such as calcium alginate (25% elemental Ca), calcium lactate (12%), and calcium gluconate (8%). Dialysis patients should avoid calcium chloride because it may induce metabolic acidosis. Although calcium citrate is as effective as calcium carbonate, its use should be avoided, or at least very carefully monitored, since citrate markedly enhances intestinal absorption of aluminium and increases the risk of acute aluminium toxicity.[100]

Long-term adverse effects of calcium containing phosphate binders are not known. Tumoral calcinosis and calciphylaxis are a serious concern, and it is possible that these binders may increase the incidence of such problems.[92]

Calcium Alginate

Calcium alginate is a natural polyuronic acid consisting of 1,4-L-guluronic acid in different conformations. The alginic acid is mainly isolated from brown algae, especially *Macrocystis pyrifera*. This alginic acid is usually used as a non-toxic food additive. However, in order to use it as a phosphate binder, it is charged with 80–100mg calcium per gram substance. It has been tested for its capacity as a phosphate binder *in vivo* and *in vitro* in haemodialysis patients and in CAPD patients in 1989.[101] Passlick et al. found that in 14 CAPD patients, calcium alginate did not cause significant hypercalcaemia compared with calcium carbonate. One gram of calcium alginate contains only 102mg calcium, whereas calcium carbonate contains 400 mg/g. They suggest that calcium alginate does not release calcium without binding phosphate. Patients achieved good phosphate control (1.6 mmol/L) and did not need extra aluminium supplements, although the study did not include placebo or control groups.[102]

Calcium Ketoglutarate

Calcium ketoglutarate is a semi-synthetic analogue of the amino acid glutamic acid and exerts phosphate-binding properties apparently without inducing hypercalcaemia.[103-105] Birck et al. compared it with calcium carbonate in 32 stable haemodialysis patients (20 receiving calcium ketoglutarate and 12 calcium carbonate). The incidence of severe hypercalcaemia (>2.8 mmol/L) was significantly higher in the carbonate group. Moreover, calcium keto-

glutarate showed the same phosphate binding potency as calcium carbonate and acetate.[106] However, Bro et al. reported a high incidence (29%) of gastrointestinal complaints in haemodialysis patients receiving calcium ketoglutarate.[107]

The main disadvantage of calcium ketoglutarate is its price when compared with calcium acetate or carbonate. However, in addition to its usefulness in patients prone to hypercalcaemia, it has a putative anabolic effect, which may improve malnutrition in haemodialysis patients. The rationale for this suggestion is that ketoglutarate is a central metabolite of the tricarboxylic acid cycle serving as a precursor for several non-essential amino acids. In this context, Riedel et al. found there was an increase in bodyweight as well as the phosphate control in haemodialysis patients after 12 months of calcium ketoglutarate.[103]

7.4.2 Aluminium-Containing Phosphate Binders

Before 1985, aluminium-containing phosphate binders were standard treatment for ESRD, forming insoluble and nonabsorbable aluminium phosphate precipitates in the intestinal lumen. Then the risk of toxicity from oral aluminium was appreciated and subsequently other phosphate binders have been preferred. Aluminium hydroxide dissolves rapidly and binds phosphate at any pH. The binding capacity is even greater than that of hydrogen ions. Consequently, it is acknowledged as the most effective phosphate binder *in vivo*.[108] In patients taking aluminium hydroxide, plasma aluminium levels gradually increase, although aluminium is rapidly protein-bound and deposited in tissues. The aluminium toxicity manifestations include osteomalacia, bone and muscle pain, an iron-resistant microcytic anaemia and neurological abnormalities.[109,110] Bone, brain, heart and liver are major sites of aluminium deposition in the body, but the degree of aluminium retention does not correspond with the plasma aluminium level, therefore, the desferrioxamine test is often used.[111] No safe dose of aluminium hydroxide can be identified and dialysis patients who take it even in modest doses can develop clinical evidence of aluminium toxicity.[112] In patients taking aluminium-containing phosphate binders, plasma aluminium levels should be measured monthly. Furthermore, aluminium may be especially toxic in high-risk conditions such as post-paratchyroidectomy, diabetes, low turnover bone states such as adynamic bone disease, and following reinstitution of dialysis after kidney transplantation.[113]

7.4.3 Magnesium-Containing Phosphate Binders

Fine and coworkers used the gastrointestinal washout technique to evaluate the effect of magnesium supplementation on gut phosphorus absorption. Fractional gut absorption of phosphorus decreased from 72 to 56% with 5 mmol of magnesium acetate.[114] O'Donovan and coworkers used magnesium carbonate in 28 patients for 2 years as a substitute for aluminium hydroxide. Magnesium carbonate was administered in doses of 21–63 mmol/day for the pre-study period and dialysate magnesium concentration was changed from 0.85 mmol/L to low magnesium dialysate (0.25 mmol/L). Subsequently, a significant drop in predialysis aluminium levels was observed, and serum phosphate was controlled and remained unchanged from previous levels. Magnesium levels remained between 1.01–1.33 mmol/L. All patients seemed to tolerate magnesium carbonate well.[115] Other investigators have observed the effectiveness of magnesium salts as binders but also significant gastrointestinal effects. Thus, magnesium carbonate binder together with a low magnesium dialysate is an alternative to calcium-containing binders[116] but it is not widely used.

7.4.4 Polyuronic Acid Derivatives

Synthetic hydrolysed ferrous sulfate (sodium ferrous citrate) and ferrihydrite have a significant capacity for adsorbing phosphorus. They are only slightly soluble in the gastrointestinal tract preventing excessive uptake of iron and this would make them good candidates for phosphate binding. In a study by Ritz et al., there was a median percentage decrease of serum phosphate of 20%, with a concomitant decrease in urinary phosphate excretion. Altered bowel habit was the only reported adverse effect.[117] The use of cross-linked iron dextran has been reported in haemodialysis patients. An added advantage may result from the small amount of iron

absorbed by these often chronically iron-deficient patients. Unfortunately, there is little experience with their use.[118,119]

7.4.5 Zirconyl Chloride Octahydrate

Zirconyl chloride octahydrate has been evaluated as a dietary phosphate binder in rats. It appeared to be as effective as aluminium chloride and reduced bone phosphorus burden significantly. The urinary excretion of phosphate indicated significant phosphate depletion and not even traces of zirconyl could be determined in a variety of tissues, suggesting zero gastrointestinal absorption.[120] It seems a potentially promising phosphate binder but no further development has occurred, probably as a result of difficulty in patenting it as a binder.

7.4.6 Sevelamer

Sevelamer is a water-absorbing, nonabsorbed, hydrogel-cross-linked polyallylamine hydrochloride that is free of aluminium and calcium. It is thought to be completely resistant to digestive degradation and therefore not absorbed from the intestinal tract. As a binder, it is at least as effective as calcium acetate but because of its structure it also binds certain fat-soluble vitamins such as 1,25 dihydroxyvitamin D3 and vitamin K.[121] The long-term consequences of this remain unknown.

Studies demonstrate a significant decrease in phosphorus levels with an associated decrease in PTH.[122-125] In 172 haemodialysis patients treated for 8 weeks, serum phosphate level was effectively controlled and serum total cholesterol was lowered (4.4–3.8 mmol/L), all without the induction of hypercalcaemia.[126] The mechanism of lipid reduction is probably similar to that of cholestyramine. It generally reduces serum cholesterol by up to 15%. Other studies have shown its use to be associated with less coronary and aortic calcification [127] as well as a more favourable lipid profile. Several studies have shown sevelamer can be used safely, although diarrhoea (16%) and pain (13%) were seen in phase III crossover studies.[123] The long-term study confirmed that sevelamer is effective in lowering serum phosphate levels in haemodialysis patients with a corresponding reduction in calcium phosphate product. This beneficial effect was sustained over time.[128]

Nevertheless, the introduction of sevelamer gives clinicians a valuable tool with which to attack hyperphosphataemia without inducing hypercalcaemia but at a cost. An average dose of 4800 mg/day currently costs approximately £2200 (or approximately $US3100 or Eur3600, 2002 costs).[129] Consequently, although it has found widespread acceptance in the US, because of its high cost it is not available in a number of European countries. Clearly this will always be problematic for any newly developed pharmaceutical agent competing with a compound as inexpensive as calcium (table VI).

7.4.7 Lanthanum Carbonate

Lanthanum is a rare earth element with an atomic weight of 139Da. It is present in tap water but in minute quantities. It binds phosphate ionically at all pH values (figure 4) to form lanthanum phosphate, which is highly insoluble (table VII). *In vitro* studies suggest comparable efficacy to aluminium salts (>97%).[130] However, in rats given doses up to 2000 mg/kg bodyweight, a dose-dependent decrease in bone formation rate with osteomalacia was seen.[131] This was subsequently shown to be due to severe phosphate depletion.

Lanthanum carbonate has been studied in over 1500 haemodialysis and CAPD patients. These studies show good control of phosphate levels and Ca×P products significantly less than 5.0 mmol/L.[4] Low serum lanthanum levels were detectable in the majority of patients (0.1–0.8 ng/L). This increase was

Table VI. Daily cost of phosphate binders (British National Formulary, 2001/2002)

Agent	Daily cost (£)
Calcium acetate (3–6 tablets)	0.33–0.66
Calcium carbonate:	
Titralac (6–40 tablets)	0.10–0.62
Calcichew (3–6 tablets) [500mg]	0.30–0.61
Calcichew Forte (3–6 tablets)	0.66–1.32
Calcium 500 (3–6 tablets) [500mg]	0.30–0.61
Calcidrink granules (1 sachet) [500mg]	0.90
Aluminium hydroxide (4–20 capsules)	0.24–1.18
Sevelamer (6–12 capsules [403mg]; 3–6 tablets [800mg])	2.20–4.40

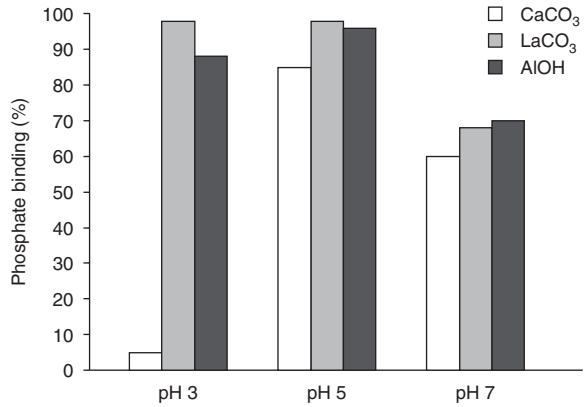

Fig. 4. Efficiency of various phosphate binders at clinically relevant pH *in vitro*.

noted for all doses administered versus baseline levels. These levels reached a plateau early in the study and showed no further increase. Furthermore, they were not dose-dependent, and no reported pathological or toxic consequences associated with the increase in plasma lanthanum concentrations of any magnitude. The incidence of adverse events was comparable to the placebo group and no safety issues were identified.[132] Bone biopsy results indicate no evidence of direct toxic effects on bone; indeed potentially beneficial changes were seen from adynamic and osteomalacic states to more normal histology after 1 year of treatment. The full results of phase IV bone biopsy studies are awaited and concern will remain about the long-term administration of a metallic element to dialysis patients. The likely cost of this agent, if it receives a product license, is not known.

8. Future Strategies

The problem of phosphate control is compounded by the fact that none of the existing phosphate binders is truly satisfactory (table VIII). Recent work has begun to explore the pathway of possible inhibition of phosphate reabsorption. The genes responsible for sodium-dependent phosphate transport have now been isolated and characterised. Research is ongoing to determine if manipulation of these transporters with novel therapeutic agents might ameliorate the hyperphosphataemia in chronic renal failure. One promising agent is phosphonoformic acid (PFA), which inhibits sodium-dependent phosphate transport. In rats with renal failure, the administration of PFA significantly increased the fractional excretion of phosphate in normal and uraemic rats, and resulted in normalisation of the plasma phosphate concentration (2.5 vs 2.1 and 1.9 mmol/L, respectively, for uraemic rats, uraemic rats with PFA and normal rats). Although the use of PFA in humans is limited by potential renal toxicity, similar therapeutic agents may prove to be effective.[133,134]

Table VII. Comparative solubility and absorption of phosphate binders

Agent	Relative Solubility	Absorption (%)
Lanthanum	1	0.02
Aluminium	9900	0.1
Calcium	29 000 000	30.0

A possible limitation to the use of agents that block phosphate reabsorption is that the rate of reabsorption is already very low in advanced renal failure. The inhibitory effect of hypersecretion of PTH on proximal phosphate reabsorption results in reduction in the fraction of the filtered phosphate that is reabsorbed from the normal 80–95% to as low as 15% in severe renal failure. Whether this residual reabsorption is mediated by sodium-phosphate cotransport and whether agents such as PFA can inhibit it are not known. PFA would also be ineffective in patients on dialysis.

Table VIII. Advantages and disadvantages of phosphate binders

Phosphate binder	Advantages	Disadvantages
Calcium carbonate	Cheap Effective	Soluble in acid pH Palatability Preparation and timing Hypercalcaemia (20–80%)[95] Large doses Calciphylaxis, vascular and soft tissue calcification GI adverse effects
Calcium acetate	Effective Cheap Soluble in both acid and alkaline pH	Poor tolerance Poor compliance Hypercalcaemia Large doses Calciphylaxis, vascular and soft tissue calcification GI adverse effects
Calcium alginate	Effective	Less hypercalcaemia Studies did not include placebo or control groups
Calcium ketoglutarate	Effective Putative anabolic effect and improves malnutrition	Expensive Not truly non calcaemic Significant GI adverse effects (29%)[107]
Aluminium salts	Binds phosphate at any pH The most effective binder Cheap	Significant toxicity Deposition in bones, brain, heart and liver No safe dose identified Regular frequent monitoring
Sevelamer	Effective Free calcium and aluminium Reduces total and LDL cholesterol Relatively safe	GI adverse effects Large doses required and probably reduced compliance No studies in CAPD or predialysis patients Very expensive
Lanthanum carbonate	Binds phosphate at any pH Effective ?Anabolic effect on bone absorption	Not licensed yet

CAPD = continuous ambulatory peritoneal dialysis; **GI** = gastrointestinal; **LDL** = low-density lipoprotein.

Daily nocturnal haemodialysis or short hours daily daytime dialysis are only likely to be suitable for a minority of home-based patients but clearly control hyperphosphataemia effectively. However, controlled studies comparing morbidity, mortality and feasibility of these alternative methods to the more traditional approaches are lacking at present.[135]

9. Conclusion

Phosphate control remains a most difficult task for nephrologists today and, if its link to increased cardiac death rates is proven, the importance of achieving it will become paramount. Until the introduction of sevelamer no significant improvements had occurred for the last two decades. Aluminium-containing binders are still in use despite the known toxicity of aluminium. The link between calcium-containing binders and coronary and aortic calcification is causing great concern amongst nephrologists. Furthermore, patients with low bone turnover are at risk of developing hypercalcaemia even if the calcium balance is only slightly positive. Sevelamer can achieve effective phosphate lowering, and is associated with less coronary and aortic calcification and lower cholesterol levels. It is a sensible option particularly for patients with long life expectancy and little chance of early transplantation. It does have several problems, such as the gastrointestinal adverse effects, large dose burden and high cost. Other promising oral phosphate binders include the polynuclear trivalent iron compounds and lanthanum carbonate. The trivalent iron based compounds are relatively cheap. Lanthanum carbonate is well tolerated and has the advantage of its anabolic effect on bones.

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