CPD with this article

Chronic Kidney Disease in Paediatrics

A focus on phosphate

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Introduction

Chronic kidney disease (CKD) refers to a state of irreversible deterioration in renal function. CKD in childhood is much rarer than in adulthood and the causes are very different. Recent published data shows an incidence of 9.3 per million age related population, and in 2013 there were 891 children less than 18 years old receiving treatment at a specialist nephrology centre.[1] The overall aim is to optimise quality of life whilst treating complications and delaying/slowing down progression of renal disease. Aggressive nutritional management is often needed to achieve optimal nutritional status and acceptable biochemistry, whilst limiting complications such as metabolic acidosis and chronic kidney disease-bone mineral disorder (CKD-BMD). Children with CKD can be a difficult group to manage, often having to combine several dietary modifications whilst trying to achieve growth. This article does not provide the scope for detailed discussion of the management of CKD in childhood, therefore management of phosphate restriction has been used to illustrate treatment strategies and challenges.

Background

In CKD, hyperphosphatemia has emerged as a risk factor for vascular calcification, cardiovascular mortality and progression of CKD.[2, 3, 4] Hyperphosphatemia occurs because of insufficient filtering of phosphate from the blood as kidney function declines.The majority of phosphate excretion (95%) occurs in the urine, with only a small amount being lost in faeces, sweat and saliva; however, this can be increased with worsening renal function to help normalise levels. Phosphate retention starts at an early stage of CKD and plays an important role in development of hyperparathyroidism. Serum phosphate levels are usually maintained until the later stages of CKD due to several compensatory mechanisms involving parathyroid hormone (PTH), fibroblast growth factor 23 and Klotho, which suppress re-absorption and increase excretion.[5, 6]

Disordered mineral and bone metabolism – CKD-BMD – is an almost universal finding with progressive CKD and presents significant obstacles to optimal bone strength, final adult height and cardiovascular health.[7, 8] Optimum growth and final adult height have been a focus for treatment for many years but, more recently, limiting the development of calcification has become a key goal as cardiovascular disease is the leading cause of mortality in both adults and children with CKD. Plasma phosphate has been identified as an independent predictor of mortality in adults. In paediatric patients it has been shown to adversely affect carotid intima media thickness and calcification.[9, 10, 11] A retrospective autopsy study of paediatric CKD patients found a high incidence of soft-tissue and vascular calcification.[12] As phosphate retention and excess calcium load are both implicated in increasing the risk of calcification, as well as cardiovascular disease and death,[7, 13, 14] The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI)[8] recommends calcium phosphate product be <55 mg^2/dL^2.

Nutritional management

Management of CKD-BMD combines the use of dietary restriction and phosphate binders. Dietary restriction should start as soon as any biochemical abnormalities are seen. KDOQI, European and NICE guidelines recommend that in CKD 4 serum phosphate should be maintained within age appropriate limits. For those patients with CKD 5, serum phosphate should be maintained between 1.3 and 1.9 mmol/L for children aged 1-12 years, and between 1.1-1.8 mmol/L during adolescence.[15, 16] In controlled studies of children and adults dietary phosphorus restriction has been shown to result in decreased serum PTH and increased 1, 25-dihydroxyvitamin D.[17]

KDOQI guidelines recommend that in children with CKD stages 3-5 and 5D, dietary phosphorus intakes should be reduced to 100 per cent of the dietary reference intakes (DRI) for age when PTH is above target levels and serum phosphate is within the normal range. When both are above the normal range for age phosphate intake should be reduced further to 80 per cent DRI.[15] Most centres in the UK base phosphate allowance on weight rather than age (see **Table One**). These allowances tend to be more generous than the KDOQI guidelines, especially in babies where the recommended phosphate intake can be as low as 80 mg/day. Practically this would be hard to achieve, even with a specialised renal formula, as 80 mg is the equivalent of 500 ml breast milk or specialist renal formula, or 300 ml of a standard whey-based formula, and most babies aged 0-6 months will need more than this to grow. There is no strong evidence to support either guidelines and it is always important to remember that guidelines should always be adjusted in line with a patient's biochemistry

Dietary restriction in children needs to reduce phosphate intake whilst ensuring adequate protein intake to ensure optimum grow.

Table One: Phosphate Allowance

Age	KDOQI Guidelines 2008 80% DRI mg/day	Current Guidelines used in most UK centres mg/day
0-6 months	80	<400 (<10 kg)
7-12 months	220	<400 (<10 kg)
1-3 years	370	<400 (<10 kg) <600 (<10-20 kg)
4-8 years	400	<800 (20-40 kg)
9-18 years	1000	<1000 (>40 kg)

Protein intake should be maintained at or above the minimum recommended level and needs to take into account protein losses from dialysate. Dietary advice should be individualised, taking into account learning needs and individual preferences. Biochemistry should be regularly monitored and advice adjusted accordingly.

Phosphate is present in high amounts in animal protein-based foods, such as meat and fish, dairy products, whole grains and nuts. In young infants with CKD, phosphorus control can be achieved by manipulation of their formulas. If breast milk is unavailable whey-based formulas contain the lowest amount of phosphate and infants are usually encouraged to continue these until 18-36 months, delaying the introduction of phosphorus rich cows' milk. If serum levels continue to be raised, specialised renal formulas with a low phosphate content can be introduced. As these formulas are also low in potassium and calcium, careful monitoring is necessary. Most foods contain some phosphate but milk and milk products normally contribute a significant amount of phosphate to a child's diet. The latest National Diet and Nutrition survey found that on average 25-30 per cent of a child's phosphate intake came from milk and milk products, 25 per cent from cereal and cereal products, and 20 per cent from meat and meat products. Children are generally given an allowance of milk and dairy foods in order to reduce their phosphate intake. Low protein milks, such as Sno-pro, Renamil and Prozero, used for metabolic patients are significantly lower in phosphate than cows' milk and can be used as a milk substitute. Although cereals and cereal products make up 25 per cent of a child's diet, intestinal absorption of phosphorus per gram of plant protein is generally less than per gram of animal based protein. Phosphorus in plants is mostly in the form of phytic acid or phytate making the bioavailability less than 50 per cent.[18, 19] Restriction of these products may not need to be so severe. Some of our families prefer to work in terms of exchanges to restrict phosphate, a list of exchanges and an exchange allowance are given to these patients. This is adjusted at each clinic visit depending on plasma levels. Families are encouraged to choose foods which are good sources of protein but contain less phosphate to reduce the risk of protein malnutrition.

The addition of phosphate to many manufactured foods is now providing a significant challenge for patients with renal disease, as it represents a 'hidden' phosphate load and could represent the main source of dietary phosphate for some patients. Phosphate is commonly added to processed meat and cheese, freeze dried foods, bakery products and beverages to enhance flavour, improve colour and extend the shelf life. Depending on food choices phosphate additives may increase phosphate intake by as much as 600 mg to 1 g per day.[20, 21] The use of phosphate additives can significantly increase the phosphate content of a food. A number of studies have demonstrated the impact of additives. Sullivan demonstrated that the mean content of phosphate in foods with a phosphate additive was 14.9 mg/g compared to 9 mg/g in the items without a phosphate additive. Sherman found a 70 per cent increase in the phosphate content of a food when an additive was present.[22, 23, 24] Inorganic phosphate from additives has a much higher bioavailability, resulting in more than 90 per cent absorption, compared with only 40-60 per cent for naturally occurring phosphorus.[25] As the phosphorus from additives is more readily absorbed they will have a greater effect on hyperphosphatemia than an equivalent amount of naturally occurring phosphate. Unfortunately, manufacturers do not have to include the phosphate content of foods on nutritional labels making it hard for families to determine which products are high in phosphorus. Education focused on the elimination of processed foods containing phosphate additives has been shown to be effective in dialysis patients.[21] We now educate patients to read the labels of any processed foods to check for phosphate additives (see **Table Two**). If the diet contains significant quantities of processed foods label checking can have a significant impact on phosphorous levels, reducing the need for restriction of naturally occurring phosphate which may improve dietary quality. Patient's knowledge of the phosphate content of foods is often lower compared to other nutrients, such as protein and potassium, therefore repeated education is necessary.[26]

Compliance with dietary restriction in children can be limited as most of their favourite foods are rich in phosphate. If levels continue to remain high once dietary restriction has been initiated phosphate binders are introduced. Phosphate binders work by blocking the intestinal absorption of phosphate. For children and young people a calcium-based phosphate binder is used as the first line treatment in addition to dietary restriction because they are safe and effective in lowering serum phosphate and PTH levels and cause the least clinical symptoms of all the binders.[5, 27, 28]

Children are generally given an allowance of milk and dairy foods in order to reduce their phosphate intake.

Table Two: Phosphate Additives

• Phosphoric acid	• Hexametaphosphate	• Monophosphates	• Calcium Phosphates
• Pyrophosphate	• Sodium aluminiumphosphate	• Diphosphates	• Sodium phosphates
• Polyphosphate	• Aluminium phosphate	• Triphosphates	• Potassium phosphates

They provide an additional source of calcium, as approximately 20-30 per cent of the calcium in the binder is absorbed; this can be a useful as calcium intake is often compromised when restricting phosphate. Children should be advised to take their binders immediately before a meal as a lower pH improves binding capacity. They should not be taken with iron supplements as iron impairs absorption; iron therapy may impact on compliance due to the frequency of administration across the day. Children may struggle to fit both iron and phosphate binders into the daily routine. Compliance with phosphate binders is a major issue due to size, palatability, number of tablets and frequency they have to be taken. An audit survey of phosphate binder compliance in Alder Hey patients with CKD 4-5 found that over 50 per cent of patients admitted not taking at least one dose of their phosphate binders each day. Following the survey, a phosphate binder starter pack was introduced, which contains several different types of calcium carbonate (see **Table Three** for examples) for the children to try and choose the best option for them, this has improved compliance. The main issue with calcium containing binders is that they can cause hypercalcaemia and atopic calcification. If calcification is a concern, indicated by rising serum calcium levels, calcium containing binders are reduced or stopped; if the patient is old enough a non-calcium binder, sevelamer hydrochloride is introduced. It is also recommended that the total intake of elemental calcium, including diet, should not exceed 2 x DRI. Lanthanum carbonate has been used in adults for several years and is an effective phosphate binder, it has not been approved for use in children as the long-term consequences of its accumulation in the body remain unknown.

Conclusion

Keeping phosphate levels well controlled can be challenging for families and healthcare professionals, especially with the increasing use of phosphate additives by the food industry. Dietary advice should be tailored to individual patient needs, along with ensuring that they still maintain an adequate protein intake. Phosphate binders should be introduced if dietary restriction is not sufficient to control serum levels, although, compliance remains a considerable problem. As our understanding on the mechanism of CKD-BMD increases our advice may change, and we may need to introduce dietary changes at a much earlier stage of CKD.

Table Three: Types of Calcium Carbonate

Preparation	Elemental Calcium mg	Estimated potential binding capacity
Calcium Carbonate		Approximately 39 mg phosphate per 1 g Ca carbonate
Adcal	600	
Calcichew	500	
Rennies	272	
Remegel	320	
Tums	200	
Ca carbonate solution (20%)	400	
Calcium Acetate		Approximately 45 mg phosphate per 1 g Ca acetate
Phosex tablet 1000	250	
Phosex tablet 500	125	
Sevelamer		Approximately 80 mg phosphate per 1 g sevelamar
Sevelamer hydrochloride	0	
Renagel tablet 800	0	
Renavel 800 mg	0	
Renavel powder 2.4 g	0	

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