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Oral phosphate binders

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Hyperphosphatemia is an inevitable consequence of end-stage chronic kidney disease and is present in the majority of dialysis patients. Hyperphosphatemia is observationally and statistically associated with increased cardiovascular mortality among dialysis patients. Dietary restriction of phosphate and current dialysis modalities are not sufficiently effective to maintain serum phosphate levels within the recommended range, so the majority of dialysis patients require oral phosphate binders. However, the benefits of achieving the recommended range have yet to be shown prospectively. Unfortunately, conventional phosphate binders are not reliably effective and are associated with a range of limitations and side effects. Aluminum-containing agents are highly efficient but no longer widely used because of proven toxicity. Calcium-based salts are inexpensive, effective, and most widely used, but there is now concern about their association with hypercalcemia and vascular calcification. Sevelamer hydrochloride is associated with fewer adverse effects, but a large pill burden and high cost are limiting factors to its wider use. Lanthanum carbonate is another non-aluminum, calcium-free phosphate binder. Preclinical and clinical studies have shown a good safety profile, and it appears to be well tolerated and effective in reducing phosphate levels in dialysis patients; however, it is similarly expensive. Data on its safety profile over 6 years of treatment are now published. Achievement of opinion-based guidelines appears to have become an end in itself. Dialysis patient outcomes are worse than outcomes for many types of cancer, yet prospective, outcome-based randomized controlled trials are not being undertaken for reasons that are difficult to explain.

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Normal kidneys filter large amounts of organic phosphate of which more than 90% is reabsorbed by the renal tubules. Early renal dysfunction not only reduces filtered phosphate but also decreases tubular resorption, so that urinary phosphate excretion continues to match gastrointestinal absorption, and therefore there is little change in serum phosphate levels. However, as renal function deteriorates further, this homeostatic mechanism fails, resulting in progressive hyperphosphatemia.

Despite the absence of interventional randomized controlled trials (RCTs) of phosphate lowering in patients with chronic kidney disease (CKD), phosphate is now regarded as a 'uremic toxin.'[1] The demonstration of a statistical association between serum phosphate and all-cause mortality in patients on dialysis[2] has transformed the phosphate molecule from a subject of little interest 10 years ago to 'dialysis enemy number 1' today. Unfortunately, there is little evidence that phosphate control has improved significantly over the past decade, despite the development of numerous oral phosphate binders. Several factors may have contributed to this, including the difficulty of adhering to low phosphate diets and oral phosphate binder prescriptions, on a background of inadequate phosphate clearance by dialysis. Other factors such as efficacy, cost, palatability, and safety of available binders are also important (Table 1). Despite greater interest in serum phosphate, control remains poor, so that more than 36% of UK hemodialysis patients have plasma phosphate greater than 1.8 mmol/l.[3] Of equal concern is the fact that there is no evidence from RCTs that reducing serum phosphate to a specific level results in improved clinical outcomes—largely because the appropriate trials have not been undertaken.[4]

WHY SHOULD WE TREAT HYPERPHOSPHATEMIA?

Untreated hyperphosphatemia can lead to secondary hyperparathyroidism, renal bone disease, and is statistically associated with vascular calcification, increased morbidity, and mortality.[5–7] Consequently, phosphate control has become an important therapeutic target in CKD, primarily in the hope of reducing the risk of vascular calcification and cardiovascular mortality, although evidence that this is achievable is lacking. Indeed, Bushinsky[8] makes the point that 'there are no data demonstrating that a reduction of serum phosphorus will improve survival' but also notes that 'a prudent clinician cannot dismiss the compelling epidemiologic evidence and will strive to lower serum phosphorus

Table 1 | Ideal characteristics of an oral phosphate binder

High affinity for binding phosphate—low dose (pill burden) required
Rapid phosphate binding regardless of ambient pH
Low solubility
Little to no systemic absorption
Non-toxic and without side effects
Solid oral dose form
Palatable (encourages compliance)
Inexpensive

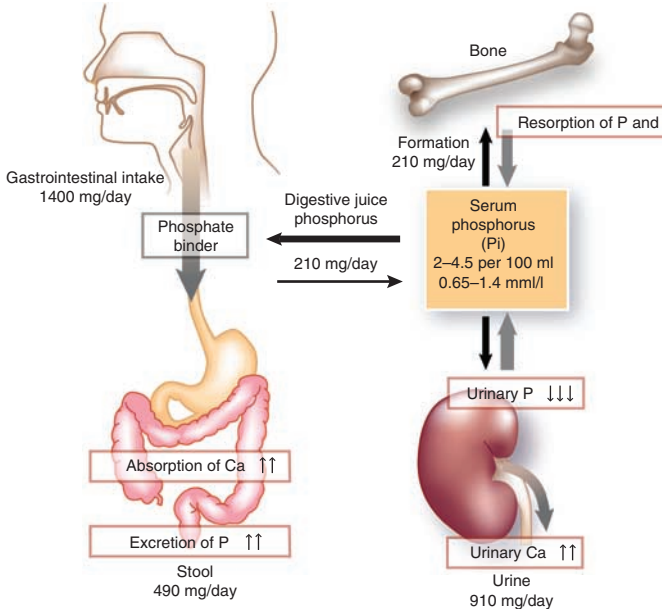

Figure 1 | Effects of oral phosphate binders.

in dialysis patients'. Consequently, hyperphosphatemia has now been added to the list of cardiovascular risk factors seen in CKD.[9]

MANAGEMENT OF HYPERPHOSPHATEMIA IN CKD

The three key elements in the management of elevated serum phosphate are dietary restriction, drug treatment using oral phosphate binders (see Figure 1), and adequate dialysis. Dietary phosphate restriction is impractical for many patients, and a general decline in home cooking skills often means that supermarkets are indirectly responsible for patients' phosphate, sodium, and potassium intake.[10,11] In addition, it can be restricted only to a certain extent without risking protein malnutrition, particularly in elderly patients.[12] Conventional 4-h, thrice-weekly hemodialysis removes approximately 1000 mg of phosphate per session, but this is generally insufficient to maintain phosphate levels within the recommended targets, even if oral phosphate intake is significantly restricted. Peritoneal dialysis removes slightly more than this when averaged over a week, but is still insufficient.[13] Although short-hours daily and slow nocturnal hemodialysis are much more effective in reducing serum phosphate levels, logistic, cost, and patient acceptance issues limit the widespread usage of these modalities.[5] Thus, around 90% of dialysis patients continue to need oral phosphate binders in an effort to control their phosphate levels.

Table 2 | Comparison of oral phosphate binders in general use

Phosphate binder	Advantages	Disadvantages
Aluminum salts	High efficacy regardless of pH Inexpensive	Aluminum toxicity No definite safe dose Frequent monitoring needed
Calcium carbonate	Aluminum free Moderately effective Moderate pill burden Inexpensive	Efficacy influenced by pH Unpalatable Hypercalcemia Gastrointestinal side effects Possible ectopic calcification
Calcium acetate	Aluminum free Efficacy somewhat pH dependent Fairly inexpensive Lower calcium load than carbonate	Large tablets need to be swallowed Hypercalcemia Gastrointestinal side effects Possible ectopic calcification
Magnesium salts	Moderate pill burden Calcium and aluminum free Moderate efficacy Moderate pill burden	Gastrointestinal side effects Not widely used Magnesium monitoring
Sevelamer	Calcium and aluminum free No gastrointestinal tract absorption Moderate efficacy Reduces total and low-density lipoprotein cholesterol	Expensive Efficacy influenced by pH High pill burden Gastrointestinal side effects Binds fat-soluble vitamins
Lanthanum carbonate	Calcium and aluminum free Chewed, not swallowed whole High efficacy regardless of pH Low pill burden	Expensive Gastrointestinal side effects Minimal gastrointestinal absorption
Magnesium iron hydroxycarbonate	Calcium and aluminum free Releases magnesium—beneficial? (Little published data)	Gastrointestinal side effects Releases magnesium—effect unknown

ORAL PHOSPHATE BINDERS

All currently available oral phosphate binders have limitations of one sort or another (Table 2) and available data from RCTs do not show the superiority of any one binder over another. Nevertheless, there has been a progressive evolution of oral binders from aluminum, through calcium salts, and on to newer agents such as sevelamer and lanthanum carbonate. The expense of the newer agents is such that it