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VASCULAR CALCIFICATION IN DIALYSIS PATIENTS

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A b s t r a c t: Renal osteodystrophy, vascular disease and mortality are believed to be linked in patients with chronic kidney disease (CKD), although to date most of the evidence is based only on statistical associations. The precise pathophysiology of vascular calcification in end stagerenal disease (ESRD) is unknown, but risk factors include age, hypertension, time on dialysis, and, most significantly, abnormalities in calcium and phosphate metabolism. Prospective studies are required before 'cause and effect' can be established with certainty, but it is an active metabolic process with inhibitors and promoters.

Clinical management of hyperphosphataemia is being made easier by the introduction of potent non-calcium based oral phosphate binders such as lanthanum carbonate. Short and long term studies have demonstrated its efficacy and safety.

Vitamin D analogues have been a disappointment as far as control of serum parathyroid hormone (PTH) levels, but evidence is emerging that vitamin D has other important metabolic effects apart from this, and may confer survival advantages to patients with CKD. Calcimimetics such as cinacalcet enable much more effective and precise control of PTH levels, but at the price of major financial burden.

Whilst it is unreasonable to expect that any one of these recent pharmacological developments will be a panacea, they provide researchers with the tools to begin to examine the complex interplay between calcium, phosphate, vitamin D and PTH such that further progress is fortunately inevitable.

Key words: dialysis, vascular calcifications, calcium phosphate binders.

Introduction

Renal osteodystrophy is recognised to be a common complication of end-stage renal failure and is believed to have its origins early in the onset of renal impairment [1]. Significant elevations of iPTH in serum have been reportted in patients with only slightly abnormal glomerular filtration rates of 60–80 ml/min [2, 3]. The skeletal manifestations vary from patient to patient, but essentially fall into two broad groups – high turnover (osteitis fibrosa and mild hyperparathyroid disease) and low turnover lesions (osteomalacia and adynamic), although one may also see mixed lesions, osteoporosis, osteosclerosis, and in children, retardation of growth. Extra-skeletal manifestations of this syndrome, such as myopathy, vascular and visceral calcification and, peripheral ischaemic necrosis are well recognised, but over the past ten years it has become apparent that there is a strong association between serum phosphate levels and vascular disease [4, 5, 6].

The majority of studies examining the relationship between mineral metabolism and vascular disease in dialysis patients have been large-scale, but retrospective and observational in nature, and clearly a statistical association does not prove 'cause and effect'. Only one prospective study has so far been reported but again it has added weight to the widely held belief that the management and control of serum phosphate, with oral calcium-containing phosphate binders, can influence vascular calcification [7]. Block demonstrated that patients who already have vascular calcification present at the time of starting dialysis, suffer more rapid progression of their calcification if treated with calcium-containing oral phosphate binders. This agrees with retrospective studies showing a positive association of calcification with serum calcium levels from low to high-normal [5, 6]. However, there is one other significant study showing quite the contrary [8]. In a prospective study of 433 haemodialysis patients, Foley and Parfrey found that relative hypocalcaemia, as a time-averaged parameter, was strongly associated with ischemic heart disease and death. These contradictions highlight the need for large, long-term prospective, interventional studies, as called for by the authors of the kDOQI Clinical Practice Guidelines for Bone Metabolism and Disease in CKD [9].

Pathophysiology of vascular calcification in CKD

The precise pathophysiology of vascular calcification in ESRD is unknown, but risk factors include age, hypertension, time on dialysis, and, most significantly, abnormalities in calcium and phosphate metabolism [4, 10]. These abnormalities must in various ways be linked to changes in the skeleton occurring as a result of osteodystrophy. Serum calcium and phosphate concentrations commonly exceed 2.4 and 2.0 mMol/L respectively in dialysis patients and

therefore calcification has traditionally been ascribed to supersaturation and subsequent precipitation of mineral ions. Recent studies have shown that vascular calcification is a regulated process similar to bone formation [11, 12]. Vascular smooth muscle cells (VSMC) in the normal artery wall express potent inhibitors of calcification, such as matrix Gla protein (MGP), whose absence results in spontaneous medial calcification [13]. In atherosclerotic calcification and diabetic Monckeberg's sclerosis, expression of these endogenous inhibitors is reduced, and VSMC express markers of both osteoblast and chondrocyte differentiation [12, 14]. Calcification is initiated in nodules by release of apoptotic bodies and matrix vesicle-like structures from VSMC that act as a focus for basic calcium-phosphate nucleation [15]. VSMC-derived matrix vesicles have been associated with calcification in vivo, but their composition and function are poorly understood [16].

Vascular calcification in ESRD is probably actively regulated. Bone matrix proteins are deposited in medial artery calcifications of ESRD patients, suggesting osteogenic conversion of resident VSMC, while in vitro studies have shown increased calcification and osteogenic changes in VSMC in the presence of elevated phosphate [17, 18]. It has also been suggested that the circulating serum protein fetuin-A, which is reduced in patients with ESRD, may play a role in regulating calcification but its mechanism of action is unclear [19].

Clinical management of hyperphosphataemia

With the advent of non-calcaemic oral phosphate binders such as lanthanum carbonate and sevelamer hydrochloride, plus the ability to vary the dialysate calcium concentration, management of serum calcium is relatively easy. This is confirmed by data from various registries as well as the DOPPS study. In contrast, serum phosphate is much more problematic. Management of hyperphosphataemia depends on three factors;

1. Dietary intake
2. Removal by dialysis
3. Binding by oral phosphate binders

Controlling dietary intake is difficult since phosphate is found within a wide variety of foodstuffs. However, reduction of phosphate-containing food additives may be possible [20]. The kinetics of phosphate removal during dialysis is incompletely understood. Phosphate is removed from both extracellular and intracellular compartments during haemodialysis so that the plasma phosphate concentration levels off after the first 1 or 2 hours of treatment and plasma concentrations can rebound even before therapy is complete [21]. It is likely that the major barrier to phosphate removal is limited transfer of phosphate between the intracellular and extracellular compartments, although other complex

factors also play important roles. Theoretical predictions suggest that increasing either treatment frequency or treatment duration can increase phosphate removal, but of course neither of these approaches is generally applicable to an in-centre dialysis population. Therefore at present the majority of dialysis patients require an oral phosphate binder, and it seems reasonable to imagine that strict control of serum phosphate and calcium by this means might decrease the likelihood of vascular calcification (or ossification as it might be called) increasing. Large-scale prospective studies are needed to examine this possibility.

Oral phosphate binders

The ideal oral phosphate binder would have the characteristics outlined in Table 1. However, as shown in Table 2, few of the available binders match these ideals. Sevelamer possesses some of the attributes, but is of limited potency which results in many patients having to take 12–15 pills or more daily. Lanthanum carbonate is a more potent agent, offering the possibility of control with only 3 pills daily, at an average dose of around 750 mg tds. It has been shown to be effective in both haemodialysis and peritoneal dialysis patients [22], in short-term [23] and long-term (three year follow-up) studies [24]. A small number of patients have taken lanthanum continuously now for over 6 years and will continue to be followed for as long as they remain on dialysis.

Although concern was raised about lanthanum's long-term effects on bone health, accumulating data suggests these fears were groundless. Concerns had been raised about the potential for accumulation of lanthanum in a similar way to aluminium, however a 2 year, prospective, multicentre study comparing the effects of lanthanum carbonate and calcium carbonate on bone did not show any evidence of harmful effects. Indeed the proportion of patients with adynamic bone, osteomalacia or hyperparathyroidism in the lanthanum group decreesed from 36% to 18% after 1 year of treatment, whereas it increased from 43% to 53% in the calcium carbonate group. [25]. Similarly reassuring results were found by Spasovski *et al* [26].

Table 1 – Табела 1

Characteristics of an ideal oral phosphate binder
Карактеристики на еден идеален орален фосфор врзувач

• High affinity for binding phosphorous – low dose required
• Rapid phosphate binding
• Low systemic absorption (preferably none)
• Non toxic
• Palatable – to encourage adherence

Table 2 – Табела 2

Advantages and Disadvantages of available oral phosphate binders
Предности и слабости на расположливите фосфор врзувачи

Phosphate binder	Advantages	Disadvantages
Calcium carbonate	Aluminium-free Moderately effective Moderate pill burden Cheap	Efficacy influenced by pH Unpalatable Hypercalcaemia GI side-effects ?ectopic calcification
Calcium acetate	Aluminium-free Efficacy somewhat pH dependant Moderately cheap Lower calcium load than carbonate	Large tablets need to be swallowed Hypercalcaemia GI side-effects ?ectopic calcification
Aluminium salts	Calcium-free High efficacy regardless of pH Cheap Not pH dependent Moderate pill burden	Aluminium toxicity No definite safe dose Frequent monitoring needed
Magnesium salts	Calcium- and aluminium-free Moderate efficacy Moderate pill burden	GI side-effects Not widely used Magnesium monitoring
Sevelamer	Calcium- and aluminium-free No GI tract absorption Moderate efficacy Reduces total and LDL cholesterol	Expensive Efficacy influenced by pH High pill burden GI side-effects Binds fat-soluble vitamins
Lanthanum carbonate	Calcium- and aluminium-free Chewed, not swallowed whole High efficacy regardless of pH Low pill burden	Expensive GI side-effects Minimal GI absorption

Entry of phosphate via the gastrointestinal tract can be further impeded by blocking its uptake at the level of the sodium dependent phosphate cotransport mechanism. Takahashi et al showed that this approach could control serum phosphate levels in a group of haemodialysis patients after stopping their calcium-based binder [27].

Adherence to prescribed oral phosphate binder regimes is known to be poor in many patients, but may be improved with education and reduction of the tablet burden. Compliance with phosphate binder therapy is often problematic

because of a combination of unpalatable preparations, the need to take them with meals, frequent changes in dose and poor understanding of their importance. Calcium preparations may contribute up to 9 tablets per day, and sevelamer up to 15 or 18 tablets per day in some patients. Lanthanum carbonate confers a definite advantage if the higher dose 1000 mg tablets are tolerated, with a realistic prescription of only 3 tablets per day.

Vitamin D analogues and Calcimimetics

Novel analogues of vitamin D offered the possibility of control of PTH without causing hypercalcaemia, but unfortunately never lived up to their initial promise. In this regard they have been completely superseded by the oral calcimimetic cinacalcet which effectively suppresses PTH in the majority of patients – albeit at a dramatic financial cost. Although perhaps no longer needed in the battle against hyperparathyroidism, there is some (once again retrospective, observational) data to suggest that vitamin D per se may improve cardiovascular outcomes in dialysis patients [28].

Data from clinical trials have demonstrated that calcimimetic therapy can reduce PTH, serum calcium and phosphorus, and the calcium-phosphorus product (Ca x P) [29] and lead to the achievement of Kidney Disease Outcomes Quality Initiative target levels for PTH and Ca x P in many more patients [30]. In addition, calcimimetics, which act through the allosteric modulation of the calcium-sensing receptor (CaR), have been shown effectively to decrease PT cell proliferation in a rat model of secondary HPT [31].

However, treatment costs also represent an issue. Treating severe SHPT with calcimimetics alone often requires high doses which may prove unsustainable for most, if not all, national health systems worldwide, while a regimen combining lower doses of a calcimimetic with injectable vitamin D might prove to be more tenable.

Conclusions

Vascular disease is now recognised to be probably the most important cause of morbidity and mortality amongst patients with CKD. Rates of vascular calcification are greatly accelerated in CKD, and the underlying mechanisms are incompletely understood. Disturbance of calcium and phosphate metabolism would appear to be an important factor and, until understanding improves, clinicians must continue to direct their efforts to control of serum levels of phosphate, PTH and calcium. New therapeutic agents are gradually making this goal look more achievable, but without prospective, randomised, interventional

studies we may never know if the guidelines currently being followed are a help or a hindrance.

Whilst it is unreasonable to expect that any one of these recent pharmacological developments will be a panacea, they provide researchers with the tools to begin to examine the complex interplay between calcium, phosphate, vitamin D and PTH such that further progress is fortunately inevitable.

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Р е з и м е

ВАСКУЛАРНИ КАЛЦИФИКАЦИИ КАЈ ДИЈАЛИЗНИТЕ ПАЦИЕНТИ

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Се верува во асоцираноста на реналната остеодистрофија, васкуларните болести и морталитет кај пациентите со хронични бубрежни заболувања, иако до денес најголемиот дел од податоците се базирани само на статистички асоцијации. Точниот патофизиолошки механизам на васкуларните калцификации кај терминалната хронична бубрежна е непознат, но во ризик факторите се вбројуваат возраста, хипертензијата, времето на дијализа, и како најзначајни се абнормалностите во метаболизмот на калциум и фосфор. Потребни се проспективни студии пред да може со сигурност да се воспостави „причинско-последичната врска“, но секако тоа е еден активен метаболен процес со присуство на инхибитори и промотори.

Клиничкото менаџирање на фосфатемијата е олеснето со внесување на потентните не-калциум базирани фосфор врзувачи како што е лантанум карбонатот. Краткотрајните и долготрајни студии ја покажаа неговата ефикасност и безбедност.

Аналозите на витаминот Д, пак, беа разочарувачки во смисла на успех во контролата на серумскиот паратироиден хормон (ПТХ), но, iznesените податоци за други метаболни ефекти на витаминот Д укажуваат на предноста во преживувањето на пациентите со хронични бубежни заболувања при нивната употреба. Калцимиметиците, како што е синакалцетот, овозможуваат многу поефективна и прецизна контрола на нивото на ПТХ, но цената претставува големо финансиско оптоварување.

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Неразумно е да се очекува дека некој од скорешните фармаколошки постигнувања ќе стане универзален лек, тие се всушност алатки за понатамошно научно истражување во комплексната интерактивност помеѓу калциумот, фосфатот, витаминот Д и ПТХ, така што понатамошниот прогрес за среќа е неизбежен.

Клучни зборови: дијализа, васкуларни калцификации, калциумски врзувачи на фосфор.

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Table 1. Characteristics of an ideal oral phosphate binder
Табела 1. Карактеристики на еден идеален орален фосфор врзувач

High affinity for binding phosphorous - low dose required
Rapid phosphate binding
Low systemic absorption (preferably none)
Non toxic
Palatable – to encourage adherence

Table 2. Advantages and Disadvantages of available oral phosphate binders
Табела 2. Предности и слабости на расположливите фосфор врзувачи

Phosphate binder	**Advantages**	**Disadvantages**
Calcium carbonate	Aluminium-free Moderately effective Moderate pill burden Cheap	Efficacy influenced by pH Unpalatable Hypercalcaemia GI side-effects ?ectopic calcification
Calcium acetate	Aluminium-free Efficacy somewhat pH dependant Moderately cheap Lower calcium load than carbonate	Large tablets need to be swallowed Hypercalcaemia GI side-effects ?ectopic calcification
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Sevelamer	Calcium- and aluminium-free No GI tract absorption Moderate efficacy Reduces total and LDL cholesterol	Expensive Efficacy influenced by pH High pill burden GI side-effects Binds fat-soluble vitamins
Lanthanum carbonate	Calcium- and aluminium-free Chewed, not swallowed whole High efficacy regardless of pH Low pill burden	Expensive GI side-effects Minimal GI absorption