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Management of Disturbances of Calcium & Phosphate Metabolism in Patients with Chronic Kidney Disease

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ABSTRACT

Management of chronic kidney disease-mineral bone disorder (CKD-MBD) can be difficult in patients with chronic kidney disease (CKD). This review aims to explain why the control of disturbed calcium, phosphate, parathyroid hormone and vitamin D metabolism is important in CKD patients. The available means to control these parameters include diet, phosphate binders, native Vitamin D, active Vitamin D derivatives and calcimimetics. However, no single measure is not enough and concerted efforts give the best result.

Keywords: Calcium and phosphate metabolism, chronic kidney disease.

INTRODUCTION

The management of calcium and phosphate metabolism in renal patients is a common problem which has been challenging nephrologists for many years. The bone mineral metabolism abnormalities that occur in renal disease are now encompassed in the term chronic kidney disease-mineral bone disorder (CKD-MBD).[1]

Compared to general population, kidney patients have an increased mortality rate[2] and around 50% of the deaths in these patients are attributable to cardiovascular causes.[3] This increased mortality may, in part, be due to the presence of one or more factors related to CKD-MBD. This review will try to answer as to why the control of calcium and phosphate is important in CKD patients and how this can be achieved.

CKD-MBD

CKD-MBD is a term describing a spectrum of abnormalities occurring in patients with renal impairment and includes derangements of bone mineral metabolism, disturbed bone turnover and vascular and soft tissue calcification.[1]

As renal disease progresses, hyperphosphataemia occurs due to decreased excretion of phosphate and also hypocalcaemia develops due to loss of 1-alphahydroxylase activity in kidney. These changes lead to secondary hyperparathyroidism resulting from positive feedback mechanism at the parathyroid gland. Raised parathyroid hormone (PTH) is required to some extent to maintain normal bone turnover as there is skeletal resistance to the hormone in renal disease.[4] Diagrammatic representation of normal homeostasis of calcium and phosphate is shown in fig. 1.

Vitamin D_3 (cholecalciferol) is formed in the skin secondary to exposure to UV light from 7-dehydrocholesterol. D_2 (ergocalciferol) is ingested as a dietary substitute. D_2 or D_3 is then hydroxylated in the liver to form 25-hydroxycholecalciferol (calcidiol) which is further

REVIEW ARTICLE

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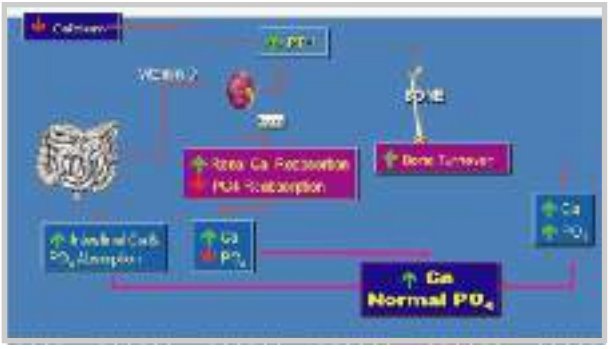

FIGURE 1: *Interrelationship between Ca & PO_4 metabolism: normal homeostatic response to decreased serum Ca.*

hydroxylated to form 1, 25-dihydroxycholecalciferol (calcitriol). Renal patients are known to have both calcidiol & calcitriol deficiencies which develop over the course of CKD.[5] The hypovitamin state of calcitriol found in CKD may also be exaggerated by an increase in levels of fibroblast growth factor 23 (FGF-23). FGF-23 is now thought to be the main regulator of phosphate homeostasis and its level rise early in CKD prior to any derangement of phosphate is detected.[6] However, FGF-23 has been shown to decrease the activity of 1-alphahydroxylase leading to less formation of active D_3 (calcitriol).[7] FGF-23 has been associated with increased mortality in patients with renal disease, independent of phosphate level, the mechanism of which remains unknown.[8]

CKD-MBD: Vascular Calcification

The other main component of CKD-MBD is calcification. Renal patients are prone to developing medial calcification of vasculature in addition to intimal calcification which is more commonly associated with atherosclerosis. Vascular calcification has been associated with increased phosphate and ingested calcium load[9] and has also been shown to predict mortality.[10] Vascular calcification is now known to be regulated by several factors.[11] The medial calcification is hypothesized to be to phenotypic changes of vascular smooth muscle cells. Hyperphosphataemia leads to the formation of osteoblast like cells in the vessel wall[12] and deposition of calcium phosphate crystals induce cell death in vascular smooth muscle cells.[13] The medial calcification that develops restricts the dilatation of the artery and hence no longer allows expansion of artery to absorb the pressure variation in cardiac cycle. This is described as vascular stiffness which has been associated with increased mortality in CKD patients.[14,15] Disturbances of calcium and phosphate metabolism in CKD patients are shown in fig 2.

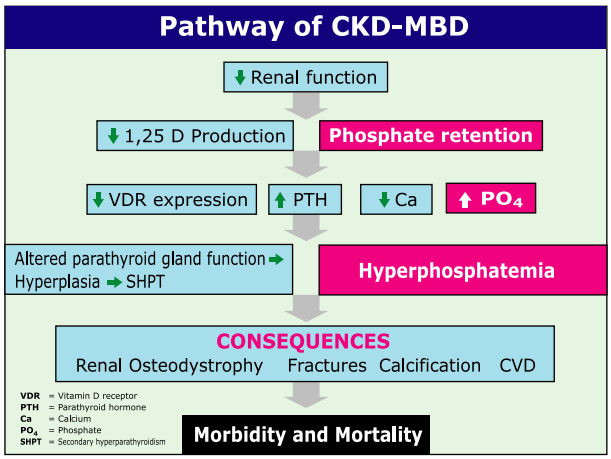

FIGURE 2: *CKD-MBD pathway.*

Management of hyperphosphataemia:

The first line therapy for hyperphosphataemia is a phosphate restricted diet. Foods rich in phosphate are milk, cheese, eggs. Phosphate binders are then introduced. Table I illustrates different phosphate binders currently available with a summary of advantages and disadvantages with each one.

Aluminium hydroxide is not routinely used for its well-known severe side effects. Calcium-containing binders are now the most common first line phosphate binders used in clinical practice. The ingested calcium load has now been shown to be associated with increased vascular calcification.[9]

The newer phosphate binders include Sevelamer hydrochloride, a resin-based binder and Lanthanum carbonate, a metal-based binder, neither containing calcium. Sevelamer hydrochloride has been shown to attenuate the progression of vascular calcification when compared to calcium- based binders.[16] The other new non calcium-based phosphate binder is lanthanum carbonate which has a potential disadvantage of being based on an elemental metal. Long-term clinical studies are reassuring.[17]

TABLE I : Phosphate Binders: Summary

Binder	Advantages	Disadvantages
Aluminum-containing	Effective	Tissue accumulation; Bone disease, encephalopathy, anemia
Calcium-containing		
Calcium acetate Calcium carbonate	Effective and widely used	Hyper-Ca, calcification risk; High pill burden
Sevelamer		
Sevelamer Hydrocloride (Renagel, Sevel) Sevelamer Carbonate (Renvela)	Less vascular calcification than Ca-containing binders; lower mortality? Reduction of TC & LDL	High pill burden (moderate potency); Cost; Tolerability
Lanthanum carbonate	Good potency;Minimal absorption; Not Hyper-Ca; Low pill burden	Cost; Taste fatigue; Unknown long term impact; Tolerability
Magnesium carbonate	Potential to minimize Ca load	Hyper-Mg; no long term studies

Management of PTH, Vitamin-D and Calcium:

Compounds used to maintain PTH, calcium and phosphate in the recommended target range are vitamin D analogues and calcimimetics. These treatments are mainly used to lower PTH levels, but vitamin-D analogues increase calcium and phosphate levels, whereas calcimimetics reduce them. So, these drugs are used in different combinations. Recommended target goals were shown in Table II.

TABLE II : K/DOQI goals for Stage 5 CKD.

Minerals	K/DOQI Range
Serum PTH	150-300 pg/ml
Serum Ca (albumin-corrected)	8.4-9.5 mg/dl
Serum P	3.5-5.5 mg/dl
Ca × P product	< 55 mg^2/dl^2

Calcitriol and 1-alphacalcidiol are the traditionally used vitamin D analogues in CKD providing replacement of the active 1, 25-dihydroxycholecalciferol. They act by negative feedback mechanism to parathyroid gland, reducing PTH. However, they also act at the receptors in the gastro-intestinal tract leading to increased absorption of calcium and phosphate. Newer vitamin-D analogues, paricalcitol and doxercalciferol produce similar effects but less persistent hypercalcaemia.[18]

Calcimimetics are novel class of drugs that act at the calcium sensing receptor to reduce PTH secretion. This therapy is associated with severe hypocalcaemia.[19] So it is only used in difficult patients whose secondary hyperparathyroidism cannot be controlled with vitamin D analogues alone and where parathyroidectomy is often the alternative. Changing the calcium content of dialysate can also be utilized to help calcium control.[20] Using the medications which have been discussed, management of each patient needs to be individually tailored to control the bone chemistry parameters.

SUMMARY & CONCLUSION:

Disordered serum calcium and phosphate have been associated with increased mortality in CKD and dialysis patients. A large number of treatment options are now available: diet, phosphate binders, vitamin-D analogues, calcimimetics, calcium content of dialysate and parathyroidectomy.[21] Good management is still a goal difficult to achieve and no single treatment is the answer.

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