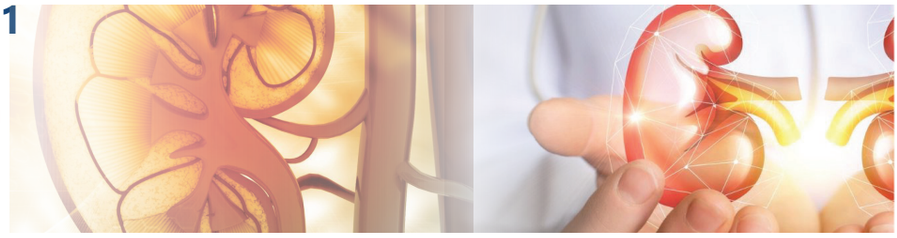
Maximising life

Volume 1 | Issue 1

CKD-MBD



Insight into the impact of vitamin D on cardiovascular outcomes in chronic kidney disease

Junarta J, Jha V, Banerjee D. *Nephrology* (Carlton). 2019 Jan 26.

Vitamin D deficiency is highly prevalent in chronic kidney disease (CKD) and is associated with increased cardiovascular mortality in both the general population and in CKD patients. Patients with chronic kidney disease (CKD) experience excess cardiovascular morbidity and mortality, usually secondary to coronary heart disease and heart failure. Patients with CKD experience excess cardiovascular morbidity and mortality that is unexplained by traditional cardiovascular risk factors; hence, the interest in non-traditional risk factors, such as vitamin D deficiency. Vitamin D has a number of extra-skeletal physiological roles, including immunomodulation and cardiovascular protection. Associations between hypovitaminosis D and increased cardiovascular mortality has been demonstrated in both the general population and in CKD.

As cardiovascular mortality is the commonest, often premature cause of mortality among those with CKD, the nephrology community has long sought for interventions that could improve the cardiovascular death in these patients. Vitamin D supplementation is reasonably safe and a simple intervention that could potentially help in this regard.

Given the excess cardiovascular morbidity and mortality CKD patients experience, it is not surprising that they demonstrate abnormal cardiovascular structure and function. About 75% of non-dialysis CKD patients display left ventricular hypertrophy (LVH), making it one of the most prominent cardiovascular abnormalities in CKD. Endothelial dysfunction, arterial stiffness, and accelerated atherosclerosis are common in CKD. Traditional and nontraditional risk factors promote the development of endothelial dysfunction, which eventually leads to the development of atheromas. Intimal and medial calcification contributes to vascular stiffness, especially in association with progressive atherosclerotic lesions.

Flow-mediated dilation (FMD), an indicator of endothelial function that measures endothelial-dependent vasodilation, predicts CVD events in CKD. The effect of vitamin D on improving endothelial dysfunction was shown by Kumar et al. in a study that provides strong evidence that the correction of vitamin D deficiency improves FMD in pre-dialysis CKD patients. Pulse wave velocity (PWV) and aortic augmentation index (AIx) evaluate arterial stiffness. PWV is an independent predictor of CVD and mortality. Kumar's group also demonstrated that D3 therapy improves PWV. Generally, those who achieved the highest serum levels of vitamin D following supplementation had the greatest improvement in PWV. The study by Kumar et al. used D3 as one of their study interventions in investigating the effect of vitamin D on endothelial dysfunction and/or vascular stiffness. The total dose of D3 over the study period used by Kumar et al., was the highest (600 000 IU), with 25(OH)D levels increasing by 24.91 ng/mL. This study was the only one that demonstrated improvements in all parameters measured. Importantly, no patient developed severe hypercalcaemia.

Meta-analyses of observational studies have shown an association between vitamin D supplementation and improvement in all-cause mortality, cardiovascular mortality, and all clinically significant end-points. Vitamin D supplementation is a reasonably safe and simple intervention and meta-analyses of observational studies have suggested that vitamin D supplementation in CKD improves cardiovascular mortality. Indeed, the meta-analysis by Duranton et al. demonstrated that active vitamin D supplementation in CKD reduced the

relative risk of cardiovascular mortality by 37%.

Looking to the future: The SIMPLIFIED trial finishes in 2025

The SIMPLIFIED trial (ISRCTN15087616) is the only ongoing RCT evaluating the impact of vitamin D supplementation on hard end-points. Study participants are randomized either to D3 therapy with a dose of 60 000 IU to be taken fortnightly or to receive normal standard care for five and a half years. The primary outcome measure is all-cause mortality which will be determined from 7 years after the start of the study. The secondary outcomes of the study include hospitalization-requiring composite cardiovascular events. This study is only recruiting adults with dialysis requiring end-stage renal disease.

More large-sized RCT like the SIMPLIFIED trial that specify hard end-points as the primary or secondary outcome are needed to assess any potential benefit with vitamin D supplementation. In addition, it is important that doses are high enough and the intervention lasts long enough before any conclusion can be drawn on the impact of supplementation on outcomes. The SIMPLIFIED trial is projected to finish in 2025 and will hopefully provide an improved understanding of the role of vitamin D supplementation in improving all-cause and cardiovascular mortality in CKD patients.

The challenge of controlling phosphorus in chronic kidney disease

Cannata-Andía JB, Martin KJ. *Nephrol Dial Transplant*. 2016 Apr;31(4):541-7.

The knowledge on the pathogenesis and management of chronic kidney disease mineral bone disorders (CKD-MBD) has grown considerably, and the diagnosis, prognosis and management of these disorders have been recently addressed in several CKD-MBD guidelines. The control of serum phosphorus at all stages of CKD is considered one of the more important aspects to improve clinical outcomes in CKD-MBD.

Serum phosphorus in chronic kidney disease

In clinical and experimental studies, high phosphorus has been associated with several negative outcomes of CKD-MBD, such as parathyroid hyperplasia, progression of CKD, increased peripheral arterial stiffness, endothelial dysfunction, vascular calcification, cardiovascular disease, infections and decreased bone strength and bone mass with increased rate of fragility, bone fractures and a higher mortality risk. It is generally accepted that the accumulation of phosphorus appears to begin in CKD Stage 3b and progresses accordingly as renal function worsens leading to a clear trend of positive phosphorus balance, which is the basis of the therapeutic strategies used to treat hyperphosphatemia. The control of serum phosphorus at all stages of CKD is therefore considered one of the more important aspects to improve clinical outcomes in CKD-MBD.

Control hyperphosphatemia in CKD

In an effort to control and treat CKD-MBD, interventions to affect phosphate homeostasis are clearly warranted. There are four main strategies to manipulate phosphate homeostasis and the consequent compensatory changes in patients with CKD. These include :

i. dietary phosphate restriction

ii. administration of phosphate binders

iii. effective control of hyperparathyroidism and

iv. in ESRD, ensuring adequacy of dialysis and the choice of dialysis regimen.

Dietary phosphate restriction

Effective dietary phosphate restriction is difficult in clinical practice. Marked dietary phosphate restriction will also result in protein restriction, which may not be desirable. Data demonstrate that the source of protein has a significant effect on phosphorus homeostasis in patients with CKD and point out the difficulty in prescribing a phosphate-restricted diet, in that bioavailability of phosphate needs to be considered rather than simply the phosphate content. An additional difficulty in achieving dietary phosphate restriction has recently been emphasized with the realization that many sources of processed foods contain additional phosphate salts, which have been added to preserve color and shelf life, and accordingly, this issue further complicates dietary counseling because the actual phosphate content, due to these added salts, may not be readily apparent. Currently, there is no requirement to label processed foods with phosphate content, which makes efforts to decrease phosphorus intake quite difficult.

Use of phosphate binders

Because of these issues with dietary phosphate restriction, the use of phosphate binders has become the mainstay of efforts to decrease phosphate absorption from the intestine. The aluminum-based binders, although quite effective, are rarely used in current clinical practice for long-term therapy due to the risk of aluminum toxicity. In recent years there have been increasing concerns about markedly positive calcium loads, which result from the use of calcium-based phosphate binders; positive calcium loads have been associated with acceleration of progression of vascular calcification. The non-calcium-containing phosphate binders, initially sevelamer hydrochloride and later sevelamer carbonate, are now widely used and were shown to be associated with decreased rate of progression of vascular calcification compared with calcium-based binders in the 'Treat to Goal' study. An attempt to show whether this was associated with improved mortality was addressed in the DCOR study. This was a multicenter, randomized, open label, parallel designed trial to compare sevelamer hydrochloride and calcium-based phosphate binders on all-cause and cause-specific mortality in a group of 2103 prevalent dialysis patients; 1068 patients completed the study.

In a subgroup of patients more than 65 years of age, there appeared to be a significant effect of sevelamer in lowering the mortality rate. A smaller study by Block et al. examined all-cause mortality in 127 patients new to dialysis, as part of a secondary end point of a randomized trial that examined coronary artery calcification. These studies showed that mortality was significantly lower in subjects randomly assigned to sevelamer hydrochloride compared with those assigned to calcium-containing phosphate binders. This mortality benefit persisted after full multivariate adjustment. Studies by Di Iorio et al. also show that sevelamer therapy appeared to improve survival in a cohort of incident hemodialysis patients.

Jamal et al. demonstrated that non-calcium-based binders appeared to be associated with a decreased risk of all-cause mortality compared with calcium-based binders. An *a priori* subgroup analysis showed a statistically non-significant decrease in mortality in patients taking either sevelamer or lanthanum compared with those taking calcium-based phosphate binders.

Recently, two different types of phosphate-binding agents have been introduced to control hyperphosphatemia in CKD. On one hand, the combination of calcium acetate with magnesium carbonate (CaMg) is shown to be as effective as sevelamer hydrochloride to control serum phosphorus and reduce FGF-23 in hemodialysis patients. On the other hand, iron containing phosphate binders such as sucroferric oxyhydroxide and ferric citrate have been introduced and appear to be effective for the control of hyperphosphatemia in ESRD. Unlike sucroferric oxyhydroxide, Phase-3 studies have shown that ferric citrate also significantly improves serum iron measures that allowed for reduction in intravenous iron and erythropoiesis stimulating agent use. In addition, as iron deficiency, a frequent finding in CKD patients, is associated with increased FGF-23 production but decreased FGF-23 cleavage, maintaining an adequate iron status seems to be a desirable goal in these patients.

Adequacy of dialysis

Part of the therapy for hyperphosphatemia is to ensure adequacy of dialysis to adequately remove phosphorus. The use of other dialysis modalities such as peritoneal dialysis, daily dialysis or nocturnal dialysis has been associated with improved management of hyperphosphatemia and even hypophosphatemia.

The control of hyperparathyroidism

Control of hyperparathyroidism is an important consideration for the treatment of hyperphosphatemia. Following the administration of a large dose of a long-acting calcimimetic agent, velcalcetide PTH values are suppressed markedly in a dose–response fashion. These observations are also consistent with long-term studies of the oral calcimimetic agent, cinacalcet

Maximising life

HOSPIMAX Maximising Life

hydrochloride, where control of hyperparathyroidism has been associated with significant reductions in serum phosphorus.

Other strategies

An additional approach to limit the intestinal absorption of phosphate might be to target the phosphate transport mechanism in the intestines. Recent studies have suggested that nicotinic acid and related compounds, such as nicotinamide, decrease intestinal absorption of phosphorus by decreasing phosphate transport.

Looking to the future

Efforts to limit phosphate intake might be facilitated by the wide-spread labeling of the phosphorus content of foods and improved knowledge of the bioavailability of ingested phosphorus in various foods. This needs to be coupled with a campaign to increase public awareness of the issues surrounding phosphate intake. Efforts to maximize phosphate removal by dialysis should be encouraged, and consideration given to the use of additional treatments or longer treatments to facilitate phosphate removal.

Conclusion

High serum phosphorus is the most important uremia-related, non-traditional risk factor associated with vascular calcification in CKD patients and in the general population. The pathogenesis and management of chronic kidney disease mineral bone disorders (CKD-MBD) has experienced major changes, but controlling the serum phosphorus at all stages of CKD still seems to be a key factor to improve clinical outcomes.