

Perspective

Title: Vitamin D and Cardiovascular Complications of Chronic Kidney Disease – What Next?

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Figure 1

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Chronic kidney disease as a global health problem and its association with cardiovascular disease

The global prevalence of CKD is 13.4%, with 10.6% being stages 3 to 5 (1). Over the last two and a half decades CKD has become a more frequent cause of death and disability worldwide, both in developed and developing nations. According to the Global Burden of Disease Study, CKD rose up the ranks of cause of 'years of lives lost' from 19th in 1990 to 16th in 2016, and is projected to become the 5th leading cause of 'years of life lost' by 2040 (2). Most of the deaths in subjects with CKD are due to cardiovascular causes. In a large three-year follow up study, cardiovascular death rates increased from 2/100patient-years in those with eGFR >60ml/min/1.73m² to 37/100patient-years in those with eGFR <15ml/min/1.73m² (3). CKD and its complications utilise a major share of healthcare resources with a cost £1.47 billion to the UK National Health Service in 2009-10 and >\$64 billion to US Medicare in 2015

CKD and cardiovascular risk factors control

The benefits of traditional cardiovascular risk factor control demonstrated in the general population have met with limited success in patients with CKD. Firstly, risk factors such as obesity and hypertension do not demonstrate a linear relationship with cardiovascular events in CKD. Secondly, cholesterol control has not been conclusively proven to be of benefit in patients with advanced CKD. In fact, two studies in haemodialysis patients showed no benefit at all. The largest randomised trial of cholesterol control showed a reduction only in atherosclerotic events (4). Trials that target CKD-specific, non-traditional risk factors have also failed to show benefit. These include phosphate lowering with sevelamar, parathyroid hormone suppression with calcimimetics, uric acid lowering with febuxostat and correction of anaemia with erythropoietin.

Vitamin D therapy in CKD, evidence so far

Vitamin D deficiency is common in patients with CKD, reflected as low 25-hydroxy and 1,25-dihydroxy vitamin D levels. Vitamin D deficiency has been associated with higher all-cause and cardiovascular mortality in patients with CKD, just as it does in the general population. Since the discovery of the role of the kidneys in activation of vitamin D in 1970 and associated bone disease, nephrologists have been keen on supplementing 1,25 di-hydroxy vitamin D in patients with end-stage kidney disease. Meta-analysis of observational studies has shown improvement of cardiovascular and all-cause mortality following **treatment with vitamin D and its analogues supplementation** in patients with CKD (5). However adequately powered randomised controlled trials have not been conducted. Hence the impact of vitamin D therapy on cardiovascular health in patients with CKD is unknown.

Use of vitamin D in general population

There has been considerable interest in studying the effect of vitamin D therapy on cardiovascular events in the last few decades. Observational studies suggest a relationship of vitamin D deficiency with cardiovascular disease, including carotid intima-media thickness, peripheral vascular disease and cardiovascular death. Vitamin D supplementation improves blood pressure, endothelial function as measured by brachial artery flow mediated dilatation, reduces levels of inflammatory markers and lipids (particularly triglycerides) in the general population with or without vitamin D deficiency. Prior to 2017 prospective trials have examined the impact of vitamin D therapy on cardiovascular

outcomes, but only as secondary endpoints and used different doses of vitamin D. Only two studies included vitamin D deficient subjects, four out of 21 studies documented a >50% rise in vitamin D levels after supplementation, and none showed any effect on cardiovascular outcomes. In a prospective randomised trial of 5101 unselected adult patients with baseline level of 66 ± 26 nmol/L, vitamin D supplementation did not improve incident cardiovascular disease and death; or myocardial infarction, angina, heart failure and arrhythmia (6). More recently in 25,871 patients with baseline vitamin D concentration of 77 nmol/L, 2000 IU/daily of cholecalciferol did not improve cardiovascular outcomes (7). ~~There was no difference between patients with Vitamin D <50 nmol/L (n=2001) or >50 nmol/L (n=13786). Hence the true impact of adequate nutritional vitamin D supplementation in vitamin D deficient individuals remains a matter of debate.~~

Impact of vitamin D on vascular function in CKD

The impact of vitamin D therapy on vascular structure and function in patients with CKD has been tested in several trials. We demonstrated improvement in brachial artery flow mediated dilatation, from $3.1 \pm 3.3\%$ to $6.1 \pm 3.7\%$ with 600,000 units of cholecalciferol in non-diabetic CKD patients with baseline 25-hydroxy vitamin D level <75 nmol/L, over 16 weeks in non-randomised trial (8). Subsequently, we showed beneficial effects of nutritional vitamin D supplementation on brachial artery flow-mediated dilatation, markers of inflammation, arterial stiffness, parathyroid hormone, intracellular cell adhesion molecule, vascular cell adhesion molecule and E-selectin in randomised placebo-controlled trial of 120 non-diabetic patients with stage 3-4 CKD and baseline vitamin D <75 nmol/L (9). In other randomized trials, pulse wave velocity improved after 6-month supplementation with 25-hydroxy vitamin D in 119 patients with eGFR 15-45 ml/min/1.73m²; and brachial artery flow mediated dilatation improved with 12-week paricalcitol therapy in CKD 3,4 patients. On the other hand, two studies failed to find any change in flow mediated dilatation and pulse wave velocity respectively. Although the effects are inconsistent, a recent meta-analysis showed that vitamin D treatment led to an improvement of endothelial function.

Impact of vitamin D on cardiac structure and function

In two randomised placebo-controlled studies, one-year active vitamin D supplementation failed to improve cardiac structure and function in patients with CKD (10,11). One study demonstrated an improvement of left atrial volume, indicating a possible improvement in diastolic function, and small but significant improvement in the number of hospitalisations due cardiovascular events (11). Adequately-powered studies with appropriate dose of 25-hydroxy vitamin D in deficient patients have not been conducted.

Lessons from vitamin D trials in CKD

These trials tell us that a number of issues need to be considered while designing future trials of vitamin D supplementation: should we enrol all patients with CKD, or only those with vitamin D deficiency; should patients with severe deficiency (<10ng/ml) be excluded; what should be the dose and duration of vitamin D supplementation; and should there be a requirement to meet a target level.

Randomised trials in CKD patients without measurement of baseline vitamin D levels and randomised trials in the general population with baseline mean vitamin D level >50 nmol/L did not

show benefits of vitamin D supplementation; whereas left-ventricular structure and function improved in heart failure patients with baseline levels of <50 nmol/L (VINDICATE study). Hence it is logical to include patients with vitamin D levels <50 nmol/L in future studies. In the VINDICATE study, cholecalciferol 4000 units/day increased vitamin D level >100 nmol/L for 12 months without causing significant hypercalcaemia, similar to our experience with 5000 units/day (9). Hence this may be the appropriate dose for future studies.

Conclusion

Epidemiology suggest a link between of vitamin D deficiency with cardiovascular events in patients with CKD; observational cohorts and **small** randomised placebo-controlled trials have shown some benefits with supplementation, **whereas larger studies in general population (VITAL) and some in CKD (PRIMO) have not** ; **hence yet** expert guidelines such as those from Kidney Disease: Improving Global Outcomes (KDIGO) and The National Institute for Health and Care Excellence (NICE), UK do not recommend the use of vitamin D in patients with CKD to improve cardiovascular events (figure 1). In order to change practice, prospective randomised controlled trials are necessary with adequate dose and long enough duration in truly vitamin D deficient CKD patients.

Figure 1

Title: The available evidence of vitamin D therapy in chronic kidney disease patients

Legend: Though epidemiological studies suggest relationship of vitamin D deficiency with CV events, observational studies show improvement with supplementation, randomised studies improve vascular function; there is no randomised trial evidence to justify supplementation in CKD patients to improve CV in regular clinical care

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