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Vitamin K in CKD: A Game-Changer or By-Stander

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Patients with chronic kidney disease (CKD) are known to have aggressive and complex cardiovascular disease burden and the absolute risk of death increases exponentially with the stages of CKD.[1] Two major pathways in CKD that are yet to be amenable to therapeutic approaches are accelerated atherosclerosis and vascular calcification.[2] In addition to the traditional cardiovascular risk factors,[3] numerous CKD-related risk factors, including inflammation, oxidative stress, uremic toxins, and perturbed mineral metabolism can escalate vascular calcification pathogenesis and have been identified as predictors of poor cardiac outcomes and survival in patients with CKD.[4,5] Several interventions targeting mineral bone disorder and related pathways (Figure 1) have been studied but demonstrated mixed findings on intermediate outcomes such as attenuation of vascular calcification and even less evidence to translate into a meaningful cardiovascular outcome for patients with kidney failure. Despite the efficacy of phosphate binders in reducing serum phosphate, there is no clear evidence that either calcium or non-calcium based binders lead to reduction in mortality compared to placebo.[6] Calcimimetics work by modulating secondary hyperparathyroidism but failed to demonstrate a mortality benefit or regression of aortic calcification among patients undergoing dialysis.[7] Other interventions such as bisphosphonate and denosumab act by reducing calcium deposition in vascular walls but neither agent has been proven to improve vascular function or calcification scores in this cohort.[8] Nevertheless, there are limited studies utilizing these agents in patients with advanced CKD due to the anecdotal concerns of adynamic bone disease with bisphosphonate,[9] and reported severe hypocalcemia with denosumab.[S1] Another widely available intervention is magnesium, which works by inhibiting phosphate absorption from the gut, thus inhibiting hydroxyapatite formation in the vessels.[S2] A recent well-designed trial in CKD did not demonstrate an impact on the progression of vascular calcification after 12 months of magnesium supplementation.[S3] A new novel agent, SNF472, acts by selectively inhibiting hydroxyapatite formation and crystallization and has demonstrated promising efficacy in attenuating coronary artery calcification and aortic calcification in the hemodialysis population.[S4] Another agent, sodium thiosulphate acts as a calcium chelator[S5] and is mainly used in the setting of calciphylaxis. Although there are signals to support reduction in calcification burden, sodium thiosulphate is yet to demonstrate convincing evidence on improvement of calciphylaxis-associated skin lesions or on mortality.[S6] A current contemporary player in this field is vitamin K, an essential cofactor for carboxylation and activation of several potent calcification inhibitors, including osteocalcin, matrix gla protein (MGP) and gla-rich protein.[S7] Vitamin K deficiency is seen in over 50% of patients on maintenance hemodialysis[S8] with coexisting high levels of the inactive form of MGP. The findings pertaining to vitamin K supplementation to substantively reduce the inactive form of MGP opened many promises that vitamin K replacement and supplementation may be a game changer to attenuate progression of vascular calcification in CKD.

There are 2 main forms of vitamin K: (i) phylloquinone, K1 primarily found in green vegetables and (ii) menaquinone, K2 found in fermented products or following conversion from K1 in the gut by a human homologue of *Escherichia coli* prenyltransferase menA (UbiA prenyltransferase domain containing 1).[S9,S10] It is important to note that the bioavailability of vitamin K2 can be reduced with the use of phosphate binders through undesired binding in the gastrointestinal tract.[S11] Dietary intake of vitamin K

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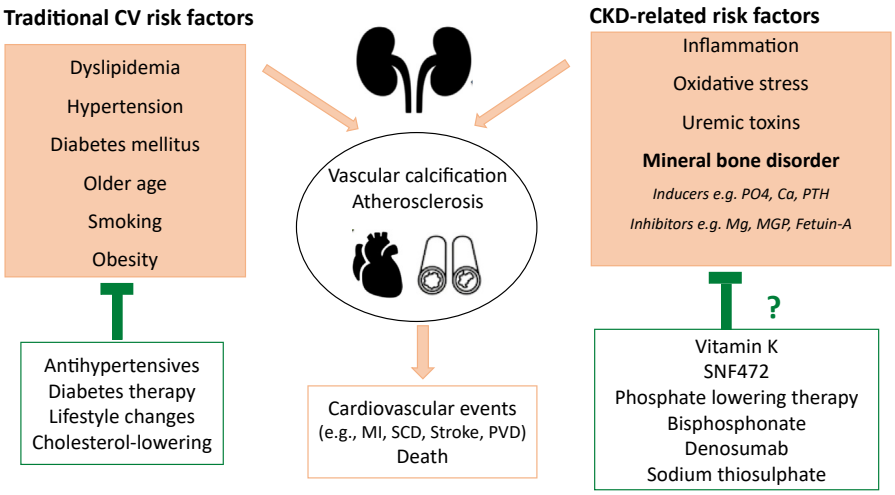

Figure 1. Cardiovascular risk factors and therapeutic approaches to vascular calcification in patients with chronic kidney disease. CKD, chronic kidney disease; CV, cardiovascular; MI, myocardial infarction; MGP, matrix gla protein; PVD, peripheral vascular disease; SCD, suddden cardiac death.

is also generally reduced in patients undergoing dialysis due to concurrent dietary potassium and phosphate restriction.[S8] Although both forms of vitamin K have been shown to have epidemiological links with adverse cardiovascular outcomes, vitamin K2 has been hypothesized to play a more substantial role in inhibition of calcification due to the longer half-life and greater levels of carboxylation of MGP compared to vitamin K1.[S12,S13] Despite these differences, vitamin K1 supplementation in the general population was shown to slow down the progression of coronary artery calcification.[S14]

In this issue, Haroon and colleagues report findings from the Treatment to Reduce Vascular Calcification in Hemodialysis Patients Using Vitamin K study.[S15] This well-executed, open-label randomized controlled trial aimed to assess whether vitamin K2 supplementation reduces progression of vascular calcification assessed by coronary artery calcification, aortic valve calcification, carotid-femoral pulse wave velocity, aortic augmentation index, and cardiovascular events. They randomized 178 patients undergoing maintenance hemodialysis to receive either oral vitamin K2 supplementation at a fixed dose of 360 μg thrice weekly on dialysis or matching placebo, of whom 138 completed the 18-month follow-up and were included in the analysis.

Despite effective reduction in the plasma levels of the inactive form of MGP, vitamin K2 supplementation did not result in a change in coronary artery or aortic valve calcification, vascular stiffness or clinical outcomes including death, major adverse cardiac events, and vascular access events. Although being a single center study that fell-short of the required sample size for the primary outcome analysis, Treatment to Reduce Vascular Calcification in Hemodialysis Patients Using Vitamin K study has several important learning points. This is the largest randomized controlled trial to date using vitamin K2 in the dialysis population that was well-designed to capture patients with preexisting high coronary calcification burden and had a comprehensive 18-month follow-up. The recruitment in a predominant Asian population further enriches and diversifies the literature on the effects of vitamin K. The secondary outcomes were relevant here because they further demonstrate minimal "signals" of the benefits of vitamin K2 on vascular calcification. Overall, the data aligns with previously published smaller randomized controlled trials of Vitamin K supplementation in the hemodialysis population[S16,S17] and more broadly with other interventions in the field of vascular calcification in the CKD population.

Despite the convincing preclinical and epidemiology data for the role vitamin K in vascular calcification,[S18] there is currently insufficient high-certainty evidence to justify the routine use of vitamin K supplementation in CKD.

Many questions are yet to be answered: it is unclear if both forms of vitamin K can be used interchangeably and if the clinical benefits might sway toward one form of vitamin K more than the other. In addition, given the complexity of the pathogenesis of vascular calcification with many vitamin K independent factors in play, a multipronged approach or more potent novel targeted biologic therapy may be the future for vascular health. Another

consideration is that vascular calcification likely reflects a state of irreversibility that may no longer be amenable to intervention, especially for patients on dialysis; and intervention at early stages of CKD may be required to prevent the occurrence of vascular calcification. Finally, vascular calcification has proven to be a challenging surrogate end point in CKD research and further studies should therefore focus on the effect of vitamin K supplementation on hard clinical endpoints. Until then, vitamin K lurks as another by-stander for cardiovascular disease management in CKD.

DISCLOSURE

The authors have declared no conflicting interests.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplemental References.

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