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Vitamin K supplementation and vascular health after kidney transplantation: Authors' response

To the Editor:

We thank Drs te Velde-Keyzer and de Borst[1] for their interest in our trial. We agree that in the small, heterogeneous cohort of kidney transplant recipients (KTR) in ViKTORIES, the lack of evidence of benefit of vitamin K supplementation does not rule out a possible role for vitamin K to improve vascular health in specific circumstances or populations. However, we note that Drs te Velde-Keyzer and de Borst do not provide evidence of any clinical trials, where this effect has been demonstrated in patients with kidney failure. Instead, they quote observational data, and a trial which demonstrated that vitamin K2 supplementation decreased desphospho-undercarboxylated Matrix Gla Protein (dp-ucMGP) in patients on dialysis, but did not assess any measure of vascular calcification.[2]

Vascular calcification is more commonly detected in KTR with cardiometabolic comorbidity.[3] ViKTORIES participants had evidence of excess vascular stiffness (higher than the expected normal range and 95% confidence limits for age and sex) and calcification (>75% of that expected for age and sex) in 27.8% and 67.8%, respectively. There was a statistical multiplicative interaction between baseline dp-ucMGP, duration of end-stage kidney disease and vascular calcification ($p = .017$), but not vascular stiffness ($p = .480$). There may be a heavier baseline burden of vascular stiffness and calcification in ViKTORIES participants than in other populations of KTR. In a recent meta-analysis, 32% of KTR had detectable vascular calcification in the abdominal aorta, though calcification severity was not consistently reported across studies.[3]

Vitamin K deficiency, as assessed by dp-ucMGP, was only detectable in our study in 32.2% of participants, though a greater proportion may have had biochemical evidence of vitamin K deficiency if we had been able to measure dp-ucMGP below 900 pmol/L. The threshold of dp-ucMGP > 500 pmol/L for vitamin K deficiency, suggested by Drs te Velde-Keyzer and de Borst,[1] is supported by a study in adults with diabetes, with and without kidney disease.[4]

Detecting vitamin K deficiency in clinical trials and clinical practice requires an available, reliable, and consistently reproducible test. dp-ucMGP is considered to be the most sensitive marker to detect subclinical vitamin K deficiency, the IDS®-iSYS InaKtif assay is the only commercially available system to measure this biomarker and the lowest calibration threshold for the assay is set at 920 pmol/L.[4] We believe that this assay needs to be more robustly calibrated to values below 900 pmol/L, particularly as the threshold for vitamin K deficiency is considered to be substantially lower.

Importantly, in two separate, recent trials of vitamin K supplementation in patients requiring dialysis (therefore similar to participants in ViKTORIES), vitamin K supplementation with vitamin K2 had no effect on coronary arterial and abdominal aortic calcification compared to placebo.[5,6]

Vitamin K supplementation provided earlier in the disease course before vascular stiffness and calcification become established, and/or in populations with clear evidence of vitamin K deficiency, may yet be associated with a clinical benefit. We, and others, have not been able to establish this in clinical trials in patients with kidney failure requiring dialysis, or in KTR.

KEYWORDS

cardiovascular disease, clinical trial, editorial/personal viewpoint, kidney disease, kidney transplantation/nephrology

DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

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