Vitamin K supplementation and vascular health after kidney transplantation

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LETTER TO THE EDITOR

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To the Editor:

We read with interest the article by Lees et al.[1] The authors conclude that in their randomized controlled trial in kidney transplant recipients (KTRs), vitamin K supplementation (menadiol diphosphate 5 mg thrice weekly) did not affect aortic distensibility or coronary artery calcium score. Although the authors deserve credit for their "Viktory" of completing this trial, and notwithstanding the relevance to publish null trial results, we question if their conclusions apply to all KTRs.

Undercarboxylation of matrix gla protein (MGP), a strong endogenous calcification inhibitor, importantly contributes to vascular calcification. Vitamin K1 and K2 are crucial cofactors to activate MGP by converting specific protein-bound glutamate residues into γ-carboxyglutamate. Vitamin K deficiency therefore results in increased plasma uncarboxylated inactive MGP proteins, including desphosphorylated-ucMGP (dp-ucMGP).[2] During the study by Lees et al, concerns were raised about assay linearity due to problems with variable recovery, particularly at the lower end of their dp-ucMGP assay (<900 pmol/L). To overcome this, dp-ucMGP values <900 pmol/L were considered equal to 900 pmol/L. This solution creates a discrepancy with previous studies that defined vitamin K deficiency as dp-ucMGP > 500 pmol/L.[2] The reported 32.2% of KTRs with baseline vitamin K deficiency is also at variance with prior studies showing a higher prevalence.[3,4] Even when defining vitamin K deficiency as dp-ucMGP >900 pmol/L, we found vitamin K deficiency in 61.4% of KTRs in our largest cohort ($N = 528$).[4]

In the study by Lees et al, biological efficacy was tested in 72/90 patients. Yet, the majority of these patients had dp-ucMGP levels <900 pmol/L at both timepoints, and were therefore defined as "900 pmol/L" (figure 2 in the paper by Lees et al).[1] Therefore, the biological efficacy seems merely based on a small subgroup of patients with more severe vitamin K deficiency. This is a concern since dp-ucMGP was the only vitamin K status marker used and the efficacy of menadiol diphosphate to improve vascular vitamin K status had not been previously studied. Moreover, the efficacy of vitamin K supplementation in a population that was in majority vitamin K-sufficient may be questioned.

At the same time, the study population included KTRs with advanced vascular calcification and stiffness. Vitamin K might be able to prevent, but not reverse, calcification and stiffness as recently shown for magnesium in vitro,[5] which may at least partly explain the null results from this trial and recent trials in other populations. In an exploratory sub-analysis by Lees et al in 29 vitamin K-deficient participants, vitamin K treatment was associated with increased aortic stiffening.[1] Although the small sample size may preclude solid conclusions, it would be relevant to know if there was interaction of vitamin K status with ESKD duration and baseline CACS/aortic distensibility, as was the case for age.

Although menadiol diphosphate did not improve the primary outcomes in the study population as a whole, the question remains whether vitamin K supplementation could be effective when given in a formulation and dose with proven biological efficacy, to a susceptible patient population. An ideal trial would target only vitamin K-deficient KTRs (dp-ucMGP > 500 pmol/L),3,4 and address whether a form of vitamin K with known efficacy (eg menaquinone-7, 360 mcg/day)6 could prevent progressive calcification in the long term (≥3 years).

KEYWORDS

cardiovascular disease, clinical research/practice, kidney disease: metabolic, kidney transplantation/nephrology, nutrition, vascular biology

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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