EDITORIAL

Vitamin K_2 for the treatment of vascular injury in patients with chronic kidney disease

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One of the biggest challenges facing patients with chronic kidney disease (CKD) is vascular calcification and rapidly progressive atherosclerosis, which results in increased mortality from cardiovascular causes and generally high mortality rates. Investigators have been searching for a solution to this problem for many years. Unfortunately, despite numerous attempts, including the use of various compounds, drug treatment is still unsatisfactory and cardiovascular complications continue to be the leading cause of death among patients with CKD. In order to provide hope for these patients, nephrologists continue to try new treatment options. A promising direction in this field of research that is currently being explored is the activation of vitamin K_2-dependent matrix Gla protein (MGP). It is a clinically meaningful endpoint in slowing the progression or inducing the regression of cardiovascular calcifications in CKD.[1] A preventive action of vitamin K in vascular calcification has been proposed based on its role in activating MGP, a calcification inhibitor that is expressed in vascular tissue. Only γ-carboxylated MGP is active and protects the vasculature from hydroxyapatite formation and deposition.[2] The activity of γ-carboxylation strictly depends on the availability of vitamin K_2.[2]

Most of the clinical trials conducted to date have focused on patients treated with renal replacement therapy. Observational clinical trials confirmed that low dietary intake of vitamin K_2 was associated with cardiovascular risk and calcification, yet on the other hand, they also demonstrated a frequent nutritional vitamin K deficiency in hemodialysis patients.[3-5] A Japanese survey among dialysis centers estimated this risk to be 11-fold higher compared with patients not receiving vitamin K antagonists.[6] In a study by Caluwé et al,[7] the clinical interventions were 3 different doses of vitamin K_2 (360, 720, and 1080 μg) thrice weekly for 8 weeks in stable dialysis patients (n = 200). Westenfeld et al[8] administered the medication as a daily oral supplement to be taken at home, Menaquinone-7 (vitamin K_2) treatment at doses of 45, 135, or 360 μg/d for 6 weeks. Data reported by Caluwé et al[7] indirectly show that supplementation of vitamin K_2 is most likely superior to efforts aiming at increasing the nutritional intake of vitamin K_2 in dialysis patients.[7] The observational Vitamin K Italian dialysis (VIKI) study on 387 patients demonstrated that vitamin K deficiency was the strongest predictor of vertebral fractures in this cohort, suggesting a potential link to other vitamin K-dependent proteins such as osteocalcin.[9] The most striking association is the warfarin-associated incidence of calciphylaxis (calcific uremic arteriolopathy) in patients with advanced renal disease.

In a prospective randomized intervention, Kurnatowska et al[10] assessed the effect of vitamin K_2 substitution on the progression of atherosclerosis and calcification by measuring specific markers in nondialyzed patients with CKD stages 3 to 5.[10] The paper contains some very interesting findings. However, as mentioned by the authors, the study has a number of limitations and some results are ambiguous and raise considerable doubts. The authors attempted to show that administration of vitamin K_2 with the addition of vitamin D alters the coronary artery calcification score and common carotid intima-media thickness (CCA-IMT) as well as a number of biochemical indices in patients suffering from CKD stages 3 to 5. Drugs were aimed at altering the concentrations of certain promoters and inhibitors of calcification and their effects seem promising. However, associating these changes with atherosclerotic progression seems too far-fetched. Unfortunately, this study has numerous limitations, as described by the authors in the discussion section, including the lack of measurement of serum vitamin K_2 concentrations. The major limitation of this study is a small sample size (n = 40) and a relatively short follow-up (270 ±12 days). The assessment of dietary intake of vitamin K also seems necessary. In a study by Caluwé et al,[7] the

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cohort size was larger and dietary intakes of both vitamins K_1 and K_2 were scrupulously recorded and estimated.

Patients in the vitamin K+D group showed a lower estimated glomerular filtration rate at baseline (eGFR; 22.4 ±10.1 ml/min/1.73 m^2) than those in the vitamin D group (30.2 ±12.6 ml/min/1.73 m^2). In addition, they showed lower serum uric acid levels, higher serum phosphate levels, higher calcium and phosphate product, and lower hemoglobin levels.[10] Variations in eGFR may have significantly affected the differences between the two groups in terms of the use of vitamins D and K_2 and, above all, the complexity and speed of atherosclerotic build-up and progression of calcification. An increase in CCA-IMT was significantly lower in the vitamin K+D group than in the vitamin D group.[10] Vitamin K_2 significantly changed the pattern of calcification promoters and inhibitors such as desphosphorylated--uncarboxylated-MGP, osteocalcin, and osteoprotegerin. However, vitamin K_2 failed to affect the progression of coronary artery calcification in CKD patients over the treatment period.[10] In a previous study, a higher carboxylation status was also stressed by a decrease in serum levels of undercarboxylated forms of osteocalcin and prothrombin during vitamin K supplementation.[8] Additionally, a stepwise multivariate linear regression analysis, performed using patients from both groups with a limited sample size, seems controversial and may require reevaluation of the results.[10] These limitations along with a few other drawbacks lower the significance of this paper by increasing the risk of overinterpretation of the results. Despite the explanation provided by the authors, it should be emphasized that vitamin K_2 and vitamin D were used despite the results referring to the group treated only with vitamin D. Such a significant difference between the groups in terms of ΔCCA-IMT after a relatively short treatment is very surprising.[10] The disadvantage is that the ultrasound evaluation was made only by 1 person (there should be 2 independent investigators). This result should be interpreted more carefully.

In summary, the study by Kurnatowska et al[10] is very interesting and casts doubt on the potential protective effect of vitamin K_2; however, it has limitations related to methods, number of patients, and especially, the lack of measurement of vitamin K_2 concentrations. Whether or not K_2-dependent MGP activation translates into the clinically meaningful endpoint of slowing the progression or inducing the regression of cardiovascular calcification in CKD is still under investigation.[1] Caluwé et al[7] and Westenfeld et al[8] demonstrated, to some extent, that biological activation of the calcification-inhibitory secretory protein MGP can be achieved by simple administration of oral vitamin K_2. Since vitamin K can practically be administered without any side effects, beside the exquisitely bad taste of vitamin K_2 supplement derived from natto, there would be numerous strong arguments supporting the liberal use of vitamin K preparations in advanced CKD.[1]

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