K-alcification Protection in Dialysis Patients: The Underestimated Phenomenon of Vitamin K Deficiency

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Calciphylaxis, or calcific uremic arteriolopathy (CUA), confronts treating physicians with an enormous challenge and a huge unmet medical need. It is a rare (orphan) but life-threatening disorder predominantly occurring in patients with end stage CKD and characterized by calcifying cutaneous arterioles and rapidly progressive, very painful skin ulcerations. Estimated 1-year mortality may range between 50% and 80% and is mostly due to superinfections with subsequent sepsis, or cardiovascular events.

Until a few years ago, CUA knowledge came from case reports and small case series, but even from this limited literature there was a strong suspicion that vitamin K antagonist (VKA) treatment may be a trigger of this disorder. This impression fits well to molecular data that the vitamin K–dependent vascular factor matrix Gla protein (MGP) represents a powerful local calcification inhibitor in the arterial wall. VKA treatment interferes with the γ-carboxylation of MGP and hence impairs its activation. The presence of active carboxylated MGP (cMGP) protects from vascular calcification, whereas undercarboxylated MGP (ucMGP) is biologically inactive. Meanwhile, surveys and registry data suggest that warfarin treatment may indeed increase the risk of CUA by a factor of 5–10-fold.5-6 Further studies are available demonstrating that patients on dialysis display an uncommonly high risk of primary (nutritional) vitamin K deficiency, even if no VKAs are administered.6

In the current pilot case-control study by Nigwekar et al.,7 the authors demonstrated that CUA patients with ESRD had proportionally higher plasma levels of the inactive ucMGP than dialysis controls. Vice versa, the authors introduce the concept that the ratio between cMGP and ucMGP, or the relative cMGP concentration, may be a key determinant of vascular calcification protection. These results strengthen the hypothesis that a strong association exists between a dysfunctional MGP system and a tendency to develop calciphylaxis. What consequences in practical patient care arise from this hypothetical link between an adequate vitamin K status and potential cardiovascular health benefits, particularly for patients with specific cardiovascular disease risk, such as those on ESRD? We feel that the time has come to discuss how to close the gaps in our evidence regarding a tailored supply of (nutritional) vitamin K and the optimal anticoagulant therapy approach (if any) in patients with ESRD.

In 2012, we published indirect evidence that vitamin K2 supplementation may indeed activate MGP in patients on dialysis.8 We demonstrated that K2 supplementation dose-dependently decreased circulating ucMGP plasma levels. At the time when our study was performed no cMGP assay was available, but as no other parameters were changed in this protocol, there was a strong probability that this observation was caused by a shift from ucMGP to active cMGP. Further, a favorable property of vitamin K supplementation is its safety because there is no risk of protein overcarboxylation: once all carboxylation sites are saturated, protein activity is 100% and cannot exaggerate further. In terms of coagulation, there would always be a balance between the activation of pro- (factors II, VII, IX, and X) and anticoagulant factors (protein S and C), and thus no procoagulatory state would ensue. Ultra-high dosage and long-term vitamin K2 (menaquinone) therapy has safely been used in osteoporosis prevention for decades, especially in Asian countries.9 In parallel or addition to vitamin K supplements, future dietary counseling could possibly educate explicitly about vitamin K-rich foods (green vegetables) and thus contribute to the reversal of vitamin K-deficient states in our patients.

Beyond optimization of vitamin K status there is even a bigger issue to be addressed: how harmful is VKA therapy to vascular wall integrity, specifically in patients with ESRD? Of note, the role of VKAs in stroke prevention in advanced CKD and specifically in ESRD with atrial fibrillation has been under critical surveillance over several years.10 There are no randomized controlled trials that demonstrate their efficacy in patients with ESRD, and disconcertingly, epidemiologic data showed increased risks of bleeding and calcification. There is hope now that some new oral anticoagulant drugs may become feasible alternatives, even for patients on dialysis,11 but we currently lack safety and efficacy data for this context.

Where do we go from here, considering that vitamin K insufficiency and/or vitamin KXA therapy stimulate the development of calciphylaxis? Nigwekar et al.7 now show data on a small cohort and with a new laboratory approach (relative cMGP concentration) which offers potential as a tool to

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steer such a therapeutic approach. However, there is still quite a way until a solid cut-off value can be identified that precisely distinguishes patients at risk from those without vitamin K deficiency, using this laboratory method. Another open question remains to what extent the plasma levels of ucMGP and cMGP reliably represent their expression ratio in the vessel wall and by what mechanisms these proteins are shed into the circulation? The standard test of functional vitamin K deficiency used in this study as a comparator, protein induced by vitamin K absence/antagonist-II (PIVKA-II), may thus be as useful and reliable in this context for the time being.

Should patients on dialysis be generally supplemented with vitamin K in the future, and if the answer is yes, with K1 or K2? Vitamin K supplementation, especially with K2 for the extrahepatic vitamin K-dependent proteins, would probably be harmless and relatively inexpensive, but randomized controlled studies with patient-centered end points will have to be performed before we can make such a recommendation. Vitamin K1 would likely work as well, because it is cycled into K2, but the required doses would have to be about ten times higher than with K2. Several proof-of-principle studies currently address the action of vitamin K1 and K2 on larger vessel (coronary and aortic) calcification progression.12–14 In case of positive results, this concept would gain quite significant attention.

One side aspect of this study warrants attention: Nigwekar et al.7 also report that CUA patients were characterized by lower 25-hydroxy-vitamin D serum levels. As a common denominator, this might of course be due to a general malnutrition affecting fat-soluble vitamins in patients with CUA. However, MGP tissue expression, and not MGP activation, is partly vitamin K-dependent.15 In future cohorts studying calcification processes in CKD, scientists should possibly also direct their attention toward the vitamin D status of included individuals, including studies and registries collecting data from patients with CUA. A causal relationship could make fat-soluble vitamin D/K coadministration an attractive standard in preventive renovascular care, if controlled studies are successfully performed and confirm this hypothesis.

In conclusion, the data basis for the detrimental input of vitamin K deficiency on extraosseous calcification processes is constantly growing stronger over time. Nigwekar et al.2 now add another important hypothesis-generating piece to this complex puzzle. Their results should strengthen any preventive measures prohibiting an inadequate vitamin K status by dietary advice, supplementation, and the avoidance of antagonism. Novel laboratory tests assessing vitamin K status appear to be within reach, but are not ready for clinical routine use yet. Vitamin K for all patients on dialysis might be the solution but its firm recommendation must still be postponed, although maybe not for much longer.

**REFERENCES**