There is a huge body of unambiguous evidence that cardiovascular calcification represents one of the most stringent mortality risk factors in patients suffering from chronic kidney disease (CKD). The more advanced the stage of CKD, the more frequently and the more severe such calcifications develop. With regard to pathophysiology, it is evident that numerous factors are involved in this process of hydroxyapatite deposition into the vessel wall, including calcium and phosphate overload, calcioprotein particles, apoptosis, osteochondrogenic trans-differentiation of the vascular smooth muscle cells (VSMCs), lack of calcification inhibitors etc. [1, 2]. One of the key calcification inhibitors is vitamin K-dependent matrix Gla protein (MGP), a 14 kDa protein exclusively expressed in chondrocytes and VSMCs [3]. MGP function appears to be sub-optimal in CKD patients and MGP may thus appear to be an appealing and promising target for vasculo-protective intervention [4]. The current pilot trial by Caluwé et al. [5] lends support to a straightforward therapeutic approach into this direction.

Several investigations tackled progression of cardiovascular calcification in the past. Substantiated calcification data in end-stage renal disease was produced by trials targeting hyperphosphataemia and hyperparathyroidism as well as studies investigating the effects of renal transplantation. The most frequently studied intervention was the comparison between calcium-containing versus calcium-free phosphate binders. While most studies in this area demonstrated superiority of calcium-free binders in this context, some did not, and especially two recent trials performed in patients in CKD stages 3b–4 raised questions about the effects of phosphate binding in such earlier stages of CKD and emphasized some safety concerns about the use and dosage of calcium-containing binders in CKD patients not on dialysis [6, 7]. However, we now have a meta-analysis of all available randomized, controlled trials (RCTs) in this context...
demonstrating that calcium-free phosphate binder use is associated with a 22% survival advantage versus use of (in relatively high doses) calcium-containing binders [8].

In the ADVANCE trial, cinacalcet-HCl was tested in haemodialysis patients in a placebo-controlled fashion in order to prevent coronary artery calcification (CAC) progression by judging the Agatston score (primary end point of the trial) [9]. Despite a trend towards a calcification-inhibitory benefit of the calcimimetic, and despite significant effects on some secondary end points (CAC progression by volume score, valvular calcification), this primary end point was not statistically significant and, thus, the ADVANCE trial must formally be considered negative. Transplantation seems to slow progression, but does not reverse pre-existing cardiovascular calcifications [10]. In general, no therapeutic approach has been associated with reversibility of established calcification so far. Therefore, there still exists an unmet need to identify clinically tolerable and effective interventions slowing down or even regressing cardiovascular damage in calcification-prone CKD patients.

MGP exists in four isoforms depending on its phosphorylation and carboxylation status [11]. Only γ-carboxylated MGP is active and protects the vasculature from hydroxyapatite formation and deposition. The activation process of γ-carboxylation strictly depends on the availability of vitamin K2. Caluwé et al. [5] now quantified dephosphorylated, undercarboxylated MGP (dp-uc-MGP) in the plasma of stable dialysis patients (n = 200), so the most inactive, but abundantly circulating isofrom, was measured here. The clinical interventions were three different doses of vitamin K2 (360, 720 and 1080 μg) thrice weekly for 8 weeks, and the expected primary end point was a decline in dp-uc-MGP levels, presumably due to increased γ-carboxylation. In the absence of a quantifiable assay for the active (and vessel bound) MGP isoform, dp-uc-MGP may be considered as one suitable biomarker reliably depicting the time course of nutritional vitamin K status in individual CKD patients.

A comparable study was recently published by Westenfeld et al. [12], and the similarities and differences should be pointed out here. Both studies clearly showed a dose-dependent decline in serum dp-uc-MGP plasma levels of similar magnitude. Higher carboxylation status was also underscored by a decrease of the serum levels of the undercarboxylated forms of osteocalcin and prothrombin (PIVKA) during vitamin K supplementation. The weekly cumulative doses of vitamin K were also similar, but Caluwé et al. administered higher single doses only thrice weekly on dialysis (in order to ascertain adherence), while Westenfeld et al. gave the medication out as a daily oral supplement to be taken at home. Caluwé et al. further had a larger cohort size and quite tediously recorded and estimated dietary intakes of both vitamin K1 and K2 when compared with the previous publication. Nevertheless, both studies confirm the power of the intervention (vitamin K2 supplementation) to sustainably change the biological activation of a key modifier of vascular calcification processes, and thus provide a feasible backbone for future RCTs to be performed.

Is there indeed a reason for treating CKD patients with vitamin K? First of all, the data by Caluwé indirectly show that supplementation of K2 is most likely superior to efforts aiming at increasing nutritional intake of K2 in dialysis patients [5]. The average nutritional intake of Belgian dialysis patients was reported to be about 15 μg/day. Thus, the highest therapeutic K2 dosage applied by Caluwé and Westenfeld, respectively, which still incompletely erased dp-ucMGP from the circulation, exceeded average daily intake by factor >20—a magnitude hardly achievable via dietary intervention.

As outlined in the paper by Caluwé et al. [3], there is straightforward experimental evidence that an intact vitamin K status may protect from vascular calcification, and that disruption by administration of vitamin K antagonists (warfarin etc.) causes rapid calcification induction. Observational clinical trials, on the one hand, supported that low dietary intake of vitamin K2 was associated with cardiovascular risk and calcification and, on the other hand, demonstrated a frequent nutritional vitamin K deficiency in haemodialysis patients [3, 4, 13]. In addition, the observational Vitamin K Italian dialysis (VIKI) study with 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 [14]. The most striking association though is the warfarin-associated incidence of calciphylaxis (calcific uraemic arteriolopathy; CUA) in patients with advanced renal disease. A Japanese survey among dialysis centres estimated this risk to be 11-fold elevated versus patients not on vitamin K antagonists [15]. The analysis of a large US database calculated a 4.3-fold CUA risk increase by warfarin treatment, and in our German calciphylaxis registry (www.calciphylaxie.de) about 50% of >200 registered patients were on warfarin therapy at the time when CUA developed [16]. Because CUA is a prototypical, rapidly aggressive and frequently lethal vascular calcification disorder, and because vitamin K can practically be administered without any side effects (besides the exquisitely bad taste of the natto-based K2 preparation), from our point of view, there would be multiple strong arguments in support of quite a liberal use of vitamin K preparations in advanced CKD.

A theoretical consideration could be the fear that high doses of vitamin K tip the balance towards hypercoagulation; however, because anticoagulant proteins S and C are activated in parallel with the procoagulant factors II, VII, IX and X and because activation in excess of 100% per molecule is physically not possible (by saturation of available γ-carboxylation site), such a scenario can be excluded. For example this is indirectly supported by Vissers et al. [17] documenting no association of vitamin K intake with ischaemic or haemorrhagic stroke in a prospective cohort of more than 35 000 healthy subjects. From an evidence-based medicine and scientific proof-of-principle point of view, any nutritional deficit replenishment therapy still needs to undergo testing for biochemical plausibility, influence upon surrogate end points and outcome data (morbidity and mortality). Medical history provides several disappointing examples regarding expectations outpacing evidence: e.g. targeting high homocysteine levels finally turned out to be a damp squib [18].

However, the nephrology community is on a consequent way filling the gaps in evidence. If vitamin K is a major switch in the prevention versus induction of vascular calcification, a standardized prospective treatment and (parallel) diagnostic...
investigation is warranted. The VitaVasK study was started just at the end of 2013, and was designed as a prospective, randomized, parallel group, multi-centre trial (EudraCT No.: 2010-021264-14) recruiting ~350 haemodialysis patients in an open-label, two-arm design [19]. CAC and thoracic aorta calcification will be quantified using multi-slice computed tomography, and patients with CAC scores of ≥100 will be randomized to continue on standard care or to receive additional supplementation with 5 mg vitamin K1 orally three times a week at the end of the dialysis session (Figure 1). Vitamin K1 can effectively replace vitamin K2 in this regard, because it is metabolized into K2, and as long as a sufficiently higher dose is given. The expectation would be that calcification progression, primarily expressed as the mean absolute difference between the thoracic aortic calcification score at the 18-month visit and the thoracic aortic calcification score at baseline, will be significantly lower in the vitamin K1 maintenance therapy group than in the standard therapy group. It needs to be pointed out though that this study is purely intended as a proof-of-principle pilot trial testing the influence of vitamin K on vascular calcification biology and will not be powered to demonstrate conclusive effects on hard outcomes. In case of a positive result, however, a large prospective trial will be the subsequent and necessary next step forward. We still believe that such a potentially positive result of this RCT would impact on clinical practice in cardiovascular prevention approaches in the CKD population, with regard to the very favourable risk-benefit-cost ratio of vitamin K supplementation.

Caluwé et al. and Westenfeld et al. indirectly, but clearly demonstrated that biological activation of the calcification-inhibitory secretory protein MGP can be achieved by simple oral vitamin K2 administration. dp-uc-MGP appears to be a suitable biomarker of this activation process as long as there are individual baseline values. Whether K2-dependent MGP activation translates into the clinically meaningful end point of slowing progression or inducing regression of cardiovascular calcification in CKD is currently under investigation.

CONFLICT OF INTEREST STATEMENT

None declared.


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The cost of ignoring acute kidney injury

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The National Confidential Enquiry into Patient Outcomes and Death (NCEPOD) Adding Insult to Injury AKI reported in 2009 that only 50% of patients who died with a diagnosis in the UK received good care [1]. This was a damning report that kick started a programme of work in the UK to better understand the syndrome of AKI, its epidemiology and impact. The journey has been an interesting one which has now been championed by the National Health Service (NHS) England as a major patient safety issue. However it is important not to lose sight of the complexity of the syndrome and continue to develop the research programme to understand the pathophysiology which will in turn drive forward the development of new therapies. The National Institute of Health and Care Excellence (NICE) AKI clinical practice guideline published in 2013 [2] will soon be followed by a quality standard to drive a quality improvement programme.

The initiatives in the UK have been driven forward by the recognition of the cost of AKI to the NHS and the potential for preventing and associated cost savings [3]. From a health economics perspective the paper published in this month’s edition of Nephrology Dialysis Transplantation by Marion Kerr et al. is an important piece of work which will support the much needed global drive to look for ways to reduce the burden of acute kidney injury (AKI). It has been made possible by the availability of national costing data in the UK which has been collected over the last 10 years in support of the current commissioning structure based around Hospital Episode Statistics (HES). It should also promote more use of this data in other disease areas.

It is now important to put the data under more detailed scrutiny by unpicking which subgroups are contributing most to the burden of illness and cost and in particular which are potentially reversible. If this could be achieved there would be an opportunity to potentially reduce the economic consequences substantially. This can only be achieved by combining the national datasets with more granular clinical data, typically collected at local level without national standardization. It is therefore imperative that there is more investment in performing more detailed retrospective audit and the prospective collection of data by national registries. This would enable healthcare professionals to start to attribute the causality of AKI and suggest optimal management/prevention strategies. Central to this process will be mapping out of the process of care in adequate detail. It must be emphasised that AKI is a syndrome with many causes and must not be all lumped together as one entity if we are to ultimately make sense of it and enable a transformational change in its management and outcomes [4].

References


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