EDITORIAL

Vitamin K in chronic kidney disease: time for a (hint of) hope?

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In 2011, we published a review in the *Polish Archives of Internal Medicine* (*Pol Arch Med Wewn*) on a series of interventional trials focused on an outcome of patients with chronic kidney disease (CKD) and end-stage kidney disease (ESRD).[1] After discussing recent clinical trials (most of which did not show benefit of applied therapeutic interventions), we prophetically concluded that the future did not look promising. More than 4 years following that publication, we can repeat that it seems that nothing works in renal patients.

As we mentioned in our paper,[1] mineral and bone disorders of chronic kidney disease (CKD--MBD) are detrimental for patients with CKD and ESRD because they simultaneously affect bone health and result in accelerated vascular calcification (which, in turn, leads to increased vascular stiffness, accelerated atherosclerosis, and premature cardiovascular morbidity and mortality). This topic was repeatedly addressed by authors publishing in the *Pol Arch Med Wewn*, including ourselves.[2-6] CKD-MBD is the promising area of intervention in patients with CKD, but also remains one of the unfulfilled hopes in their treatment. Vitamin D deficiency and elevated parathyroid hormone (PTH) are the hallmarks of CKD--MBD, and both have been identified as targets for therapeutic interventions. Nevertheless, no prospective randomized study performed to date has proved therapeutic efficacy of vitamin D supplementation (using "native" vitamin D or vitamin D analogues) or that lowering PTH using vitamin D receptor agonists (VDRA) or calcium-sensing receptor antagonists (calcimimetics) improves the outcome of patients with CKD.

We are already familiar with the results of the Evaluation of Cinacalcet Therapy to Lower Cardiovascular Events (EVOLVE) trial, designed to evaluate the effect of a calcimimetic drug, cinacalcet (extremely potent in lowering serum PTH levels), on survival and cardiovascular morbidity in more than 3800 patients on dialysis. Although some benefit could be demonstrated in post hoc analyses performed in certain subgroups of patients, the core study did not show any difference between patients randomized to cinacalcet or placebo in terms of the primary composite endpoint defined as the time until death, myocardial infarction, hospitalization for unstable angina, heart failure, or a peripheral vascular event.[7] The lack of benefit for the cardiovascular system was also demonstrated in a study comparing paricalcitol (VDRA with increased affinity to parathyroid glands) with placebo in patients with CKD stages 3 to 4. The drug failed to prevent progression of left ventricular structure and function abnormalities, as assessed by magnetic resonance imaging.[8] Hence the question of what should be used in the treatment of CKD-MBD and CKD in general to achieve a better survival of patients remains unanswered.[9]

We would like to comment on a study by Kurnatowska et al,[10] published in the current issue of the *Pol Arch Med Wewn*. In this prospective randomized double-blind study, the authors addressed one of the important pathways in vascular calcification, namely vitamin K-dependent carboxylation of matrix Gla protein (MGP). Undercarboxylated MGP promotes vascular calcification; thus, it may contribute to the development and progression of cardiovascular disease in the general population and in patients with CKD.[11,12] The authors hypothesized that supplementation of vitamin K added to vitamin D (vs vitamin D alone) may slow down the rate of progression of atherosclerosis and pathological calcification in the vasculature via enhanced carboxylation of MGP. Indeed, they were able to demonstrate that supplementation of vitamins K + D as compared with vitamin D alone in patients with CKD stages 3 to 5 was able to significantly reduce an increase in common-carotid artery intima-media thickness (CCA-IMT) just after 270 days of treatment (CCA-IMT remains a good surrogate parameter of atherosclerosis). The coronary artery calcification score (CACS) remained

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unchanged regardless of the intervention used, although the difference between the study arms showed borderline significance (with slower progression of coronary artery calcification in the vitamin K + D group) when patients with an extremely high baseline CACS were excluded from the analysis.

Despite random allocation to the treatment arms, patients randomized to the vitamin K + D group were characterized by a lower estimated glomerular filtration rate (eGFR) at baseline (ie, were at a higher risk of atherosclerosis progression). Lower hemoglobin levels in this patient group also suggested more advanced morbidity. Despite this potentially disadvantageous characteristics at baseline, the patients benefited from the combined treatment. Given the inconclusiveness of the studies evaluating the usefulness of cinacalcet, VDRA, phosphate binders, and numerous other strategies, the idea of adding vitamin K to standard treatment looks promising and deserves further research. Certainly, a relatively small size of the study group limits the conclusiveness of the data, nevertheless the results of this study may be viewed as optimistic for renal medicine.

We would also like to add a comment on recently introduced non-vitamin K antagonist oral anticoagulants (NOACs) in relation to CKD patients. NOACs seem to be at least as effective as warfarin in preventing thromboembolic events, but safer in terms of bleeding risk. Unfortunately, guidelines regarding the use of all approved drugs from this novel group uniformly state that an eGFR of less than 15 ml/min/1.72 m^2 is an absolute contraindication for their use. This means that all patients with advanced CKD who need chronic anticoagulation have no other choice than vitamin K antagonists (VKAs). Based on the results reported by Kurnatowska et al[10] and some other previously published studies, we may suspect that using VKAs may additionally harm patients with CKD, promoting vascular calcification and atherosclerosis via an interaction with MGP-dependent pathways, and, in some cases, it may result in a devastating condition known as calciphylaxis (calcific uremic arteriolopathy).[10,13,14] Unfortunately, NOACs are not an alternative option for this patient group.

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