Vascular calcification in chronic kidney disease

SUMMARY

This thesis focuses on vascular calcification in chronic kidney disease. Therefore, an explanation for the deficiency of the vascular calcification inhibitor vitamin K in these patients was investigated, and in addition, new mediators in this pathological process were studied.

In the first part of the thesis, we could observe in CKD animal model experiments that intake of the vitamin K2 isoform MK4 is significantly reduced in the context of CKD, in contrast to vitamin K1. This reveals novel directions of therapy to treat the absolute or relative (functional) vitamin K deficiency in CKD patients by supplementation therapies.

Furthermore, at the protein level we found a decrease in the enzymes HMGCR, VKORC1 and NQO1 in our CKD rat model, which negatively correlates with the degree of calcification in the kidneys. These enzymes are involved in vitamin K related processes: HMGCR is needed for the conversion of vitamin K1 to vitamin K2, and VKORC1 and NQO1 are involved in the vitamin K recycling cycle; therefore, a decrease in these enzymes might be directly linked to the deficiency of vitamin K found in CKD patients. Further studies to elucidate the decrease in the expression of these enzymes in CKD should be addressed.

In the second part of the thesis, a novel inhibitor of vascular calcification was found “VIF”. VIF has proven to be a potent inhibitor of vascular calcification in *in vitro, ex vivo* and *in vivo* models. The underlying mechanism has been described in this thesis: VIF is able to reduce the production of ROS, and the secretion of inflammatory cytokines and therefore, to impede the progression of calcification pathways. Calcium-sensing receptor is the VIF binding partner, so VIF is suggested to act as a calcimimetic of this receptor, leading to a more positive calcification outcome.

The results of this thesis revealed new reasons behind the vitamin K deficiency in CKD patients. These should be taken into account in the supplementation approaches in clinic for a better outcome of the therapy. In addition, we have found a new mediator of vascular calcification, that could open new opportunities for the development of drugs in patients with a higher risk of this pathological mechanism like CKD patients.