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TOPIC: CALCIUM-REGULATORY PROTEINS IN CKD

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Abstract

My research group tries to unravel the biological and clinical importance of calcium-regulatory proteins in uremia. In this context, low serum levels of the calcification inhibitor fetuin-A were identified as inflammation-related predictors of mortality in dialysis patients, and we recently found evidence that there seems to be an inverse relationship between fetuin-A levels and the magnitude of coronary calcifications in this patient group. In earlier stages of renal disease (CKD 1-4), fetuin-a may however act as a defense system against calcification progression, preliminary supportive evidence is currently available in diabetic individuals. Work submitted in abstract form to the 2005 ASN congress showed that sevelamer treatment is associated with delayed but long-lasting increases in fetuin-A serum levels in 41 dialysis patients. In this study, we will also include measurements of additional inhibitors such as osteoprotegerin (OPG) and matrix Gla protein (MGP) – in cooperation with Prof. Cees Vermeer, CARIM Maastricht (NL), we may soon be able to selectively detect γ -carboxylated active MGP levels. Our final aim will be to identify the value of such measurements for risk stratification in CKD patients.

We also perform experimental work in this area: Calcification-resistant fetuin-A deficient mice (C57Bl/6 background) were recently subjected to high phosphate feeding and 5/6 nephrectomy in order to mimic the CKD situation and to challenge calcification by this phenotypic constellation. We also explored the functional relevance of myocardial calcifications in calcification-prone fetuin-A deficient mice (DBA2 background) concerning ischemia tolerance and response to beta-adrenergic stimulation, and we cross-bred apoE- and fetuin-A-deficient mice to identify the influence of this phenotype on plaque calcifications. We currently test the effects of a calcimimetic compound in the DBA2 background model. Further, there is evidence that Matrix Gla protein (MGP) and osteopontin (OPN) are potentially important modifiers of fetuin-A deficiency. As a first approach, we started dietary depletion of vitamin K in order to challenge additional vascular calcification in calcification-prone fetuin-A ko mice. Finally, we explore the influence of numerous compounds including vitamin D, PTH, steroid hormones, cytokines etc. on fetuin-A expression and synthesis in vitro by using several human and rodent hepatocyte cell lines. The future goal of this approach could be the identification of substances which are capable to upregulate the endogenous fetuin-A production as a therapeutic means.

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