Calcification in the vessel wall – a role of enzymes of the vitamin K cycle?

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Introduction and aim:

Pathophysiological calcification in the vasculature favours cardio- and cerebrovascular diseases (CVD). In patients with chronic kidney disease vitamin K metabolites, particularly K1 and MK-4, are associated with decreased vascular calcification.

We investigate the expression of components of the vitamin K cycle (VKC) and the MK-4 synthesis (MKS) in vessels and bone to identify differences in expression pattern during atherosclerosis (AS) stages in aortic vascular tissue and compare these profiles in both tissue types.

Material and methods:

Gene expression levels of components of the VKC (VKOR, VKORC1L1, GGCX, the chaperone CALU) and the enzymes necessary for MKS (NQO1 and UBIAD1) were examined with predesigned TaqMan gene expression assays on a LC480 system in aorta and bone of 26 brain dead organ donors. Beta actin was used as a reference gene and relative Cp values were obtained by division.

Determination of calcification stages was done histologically: no changes: unaffected vessels, intima thickening: more than one-fold thickening of the intima without calcification, intima calcification: one or more calcification spots.

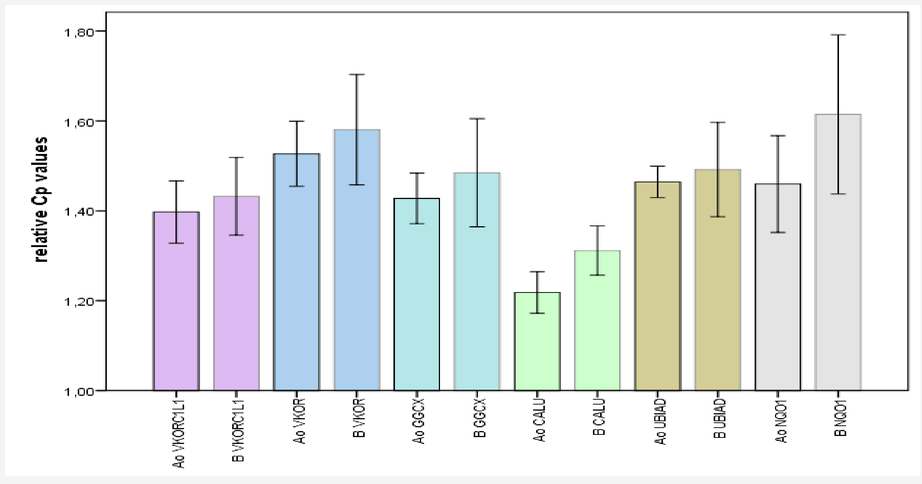


Fig.1: The enzymes of the VKC VKORC1L1, VKOR, GGCX and the chaperone CALU, and the enzymes NQO1 and UBIAD1 of the MKS are expressed in aorta and bone. Ao: aorta; B: bone, error bars: +/- 2 standard deviations.

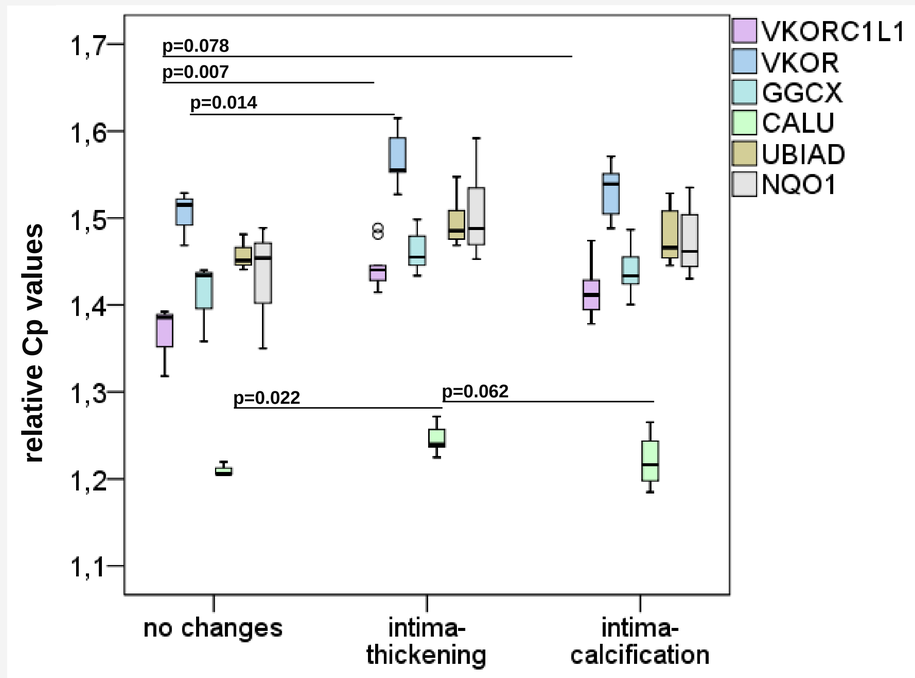
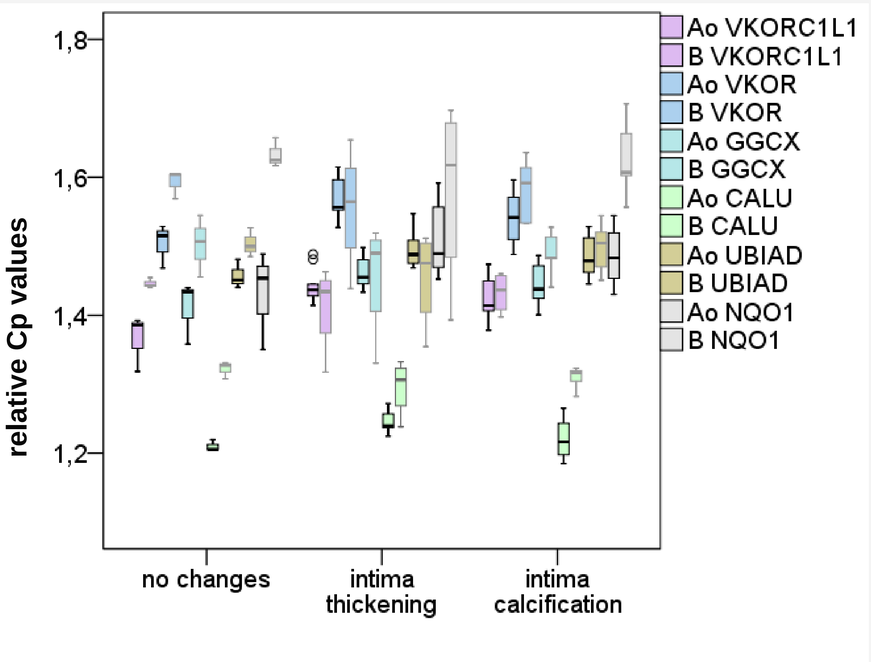


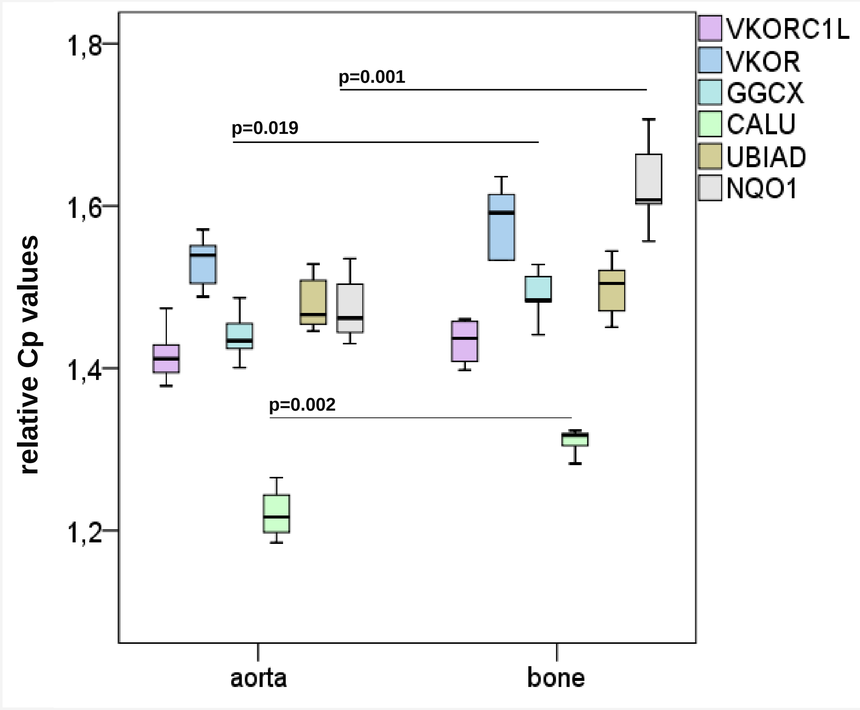
Fig.2: Gene expression of components of the VKC and of MKS in aorta in 3 stages of atherosclerosis: Gene expression of VKORC1L1, VKOR and CALU is significantly lower in the stage of intima thickening than in the unchanged vessel. Gene expression of VKORC1L1 and CALU is higher in the stage of intima calcification than in intima thickening Unchanged vessel: n=3, intima thickening n=10 and intima calcification n=10.



Ao: Aorta, black frames; B: bone, light grey frames

Fig.3: Changes in gene expression in 3 AS stages: There are no changes in gene expression in the bone during AS progression. Gene expression of VKOR, VKORC1L1 und CALU (p=0.040; p=0.023, p=0.038) in the aorta is significantly different and of GGCX (p=0.060) by trend different in the 3 AS stages.

Fig.4: Differences in gene expression in aorta and bone during intima calcification: Gene expression of GGCX, CALU and NQO1 is in bone significantly lower than in the calcified aorta. Aorta n=8; bone n=5.



Conclusion:

Gene expression of enzymes of vitamin K metabolism changes during calcification of the vessel wall.

These data might implicate a more complex role of vitamin K metabolizing enzymes in vascular calcification than previously known.

This work was supported by BioPersMed (COMET K-project 825329), which is funded by the Federal Ministry of Transport, Innovation and Technology (BMVIT) and the Federal Ministry of Economics and Labour/the Federal Ministry of Economy, Family and Youth (BMWA/BMWFJ) and the Styrian Business Promotion Agency (SFG) and the Jubiläumsfonds Project (ÖNB) 13266.

Summary:

- We show that bone and aorta express the components of MK-4 synthesis as well as of the vitamin K cycle.
- Bone and aorta express the enzymes necessary to synthesize MK-4.
- We demonstrate that a different gene expression pattern exists in AS progression in bone and aorta.
- During AS progression gene expression pattern changes in the aorta but not in bone.
- Gene expression of components of the VKC and MKS differ between bone and aorta only in the (later) stage of vessel calcification.