Calcification in the vessel wall – impact of vitamin K dependent proteins (VKDPs)

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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 classical (MGP, OC, BSP) and new vitamin K dependent proteins 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 vitamin K dependent proteins (BSP, MGP, OC, TGFBI, GRP, GAS6, periostin, protein Z, protein S, PRRG 1-4) were examined with predesigned TaqMan gene expression assays on a LC480 system in vessels (external iliac artery and 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.

Statistics. * p < 0,05; ** p >0,01; *** p>0,001

Atherosclerosis vs no atherosclerosis

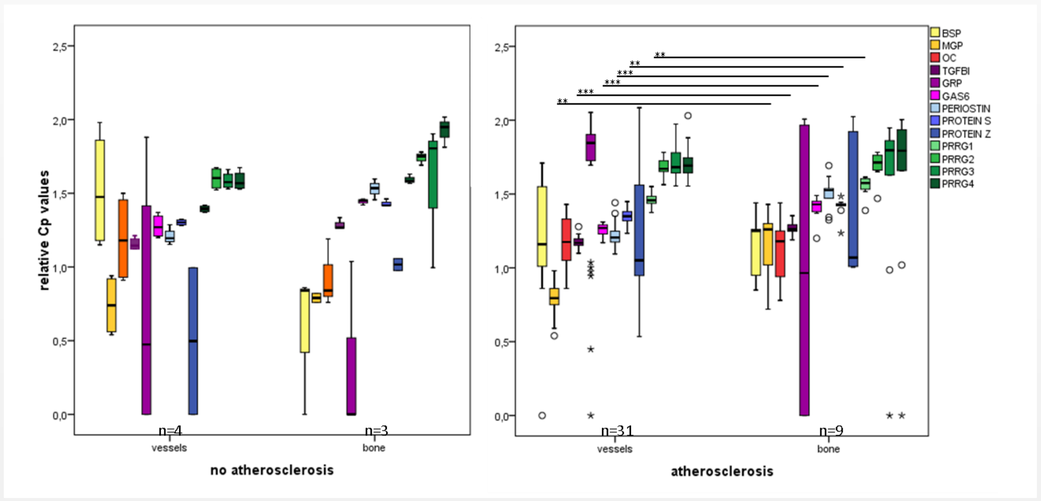

Fig.1: Comparison of gene expression of VKDPs in vessels and bone: Gene expression of MGP (p=0.001), TGFBI (p<0.001), GAS6 (p<0.001), PERIOSTIN (p<0.001), PROTEIN S (p=0.001) and PRRG1 (p=0.001) decreased in bone compared to vessels in atherosclerosis.

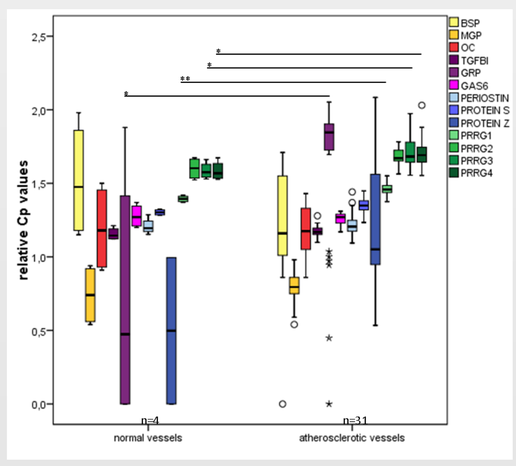

Fig.2: Gene expression of VKDPs in vessels: Gene expression of GRP, PRRG1, 3 and 4 are significantly decreased in atherosclerosis compared to normal state (p=0.037, p=0.002, p=0.011 and p=0.011, respectively).

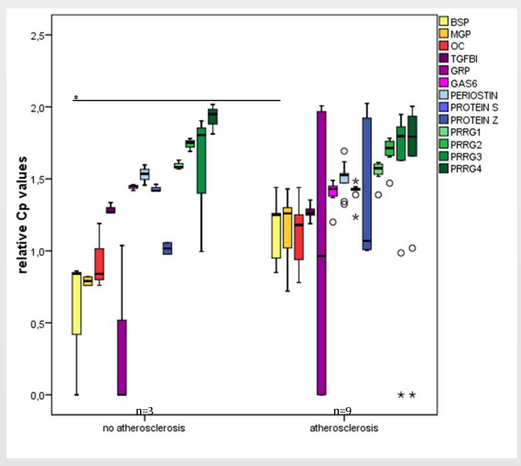

Fig.3: Gene expression of VKDPs in bone: Gene expression of BSP significantly decreased (p=0.018) when atherosclerosis in vessels is present.

Atherosclerosis progression

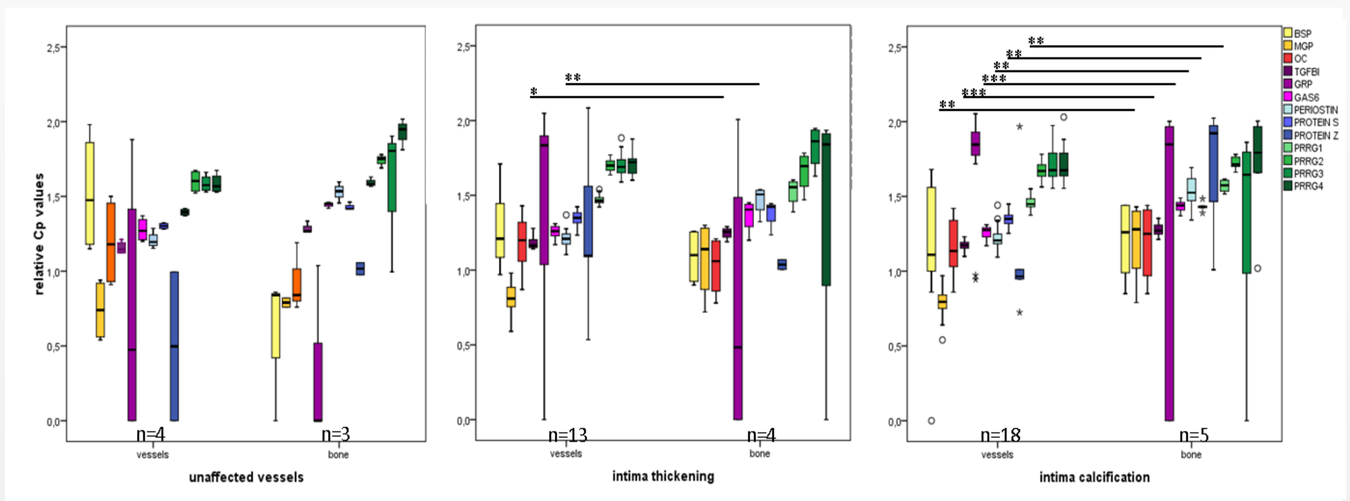

Fig.4: Comparison of gene expression of VKDPs in vessels and bone in three stages of atherosclerosis: Differences in gene expression of TGFBI (p=0.023) and PERIOSTIN (p=0.002) are seen in intima thickening, in intima calcification also MGP (p=0.007), GAS6 (p<0.001), protein S (p=0.002) and PRRG1 (p=0.001) show differences in gene expression in bone and vessels.

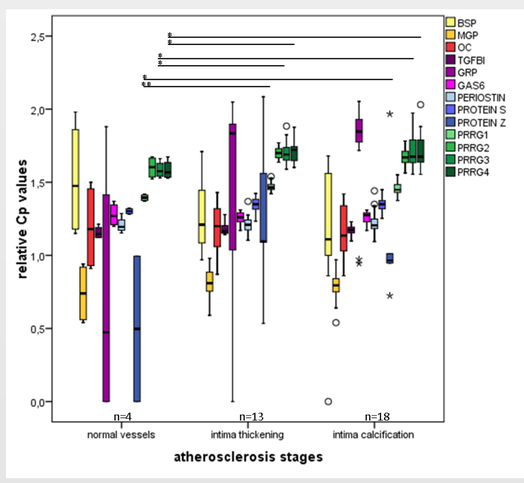

Fig.5: Changes in gene expression of VKDPs in vessels in 3 AS stages: PRRG1,3 and 4 gene expression decreased during intima thickening (p=0.013, p=0.048 and p=0.049, respectively) and keeps low in the calcification stage.

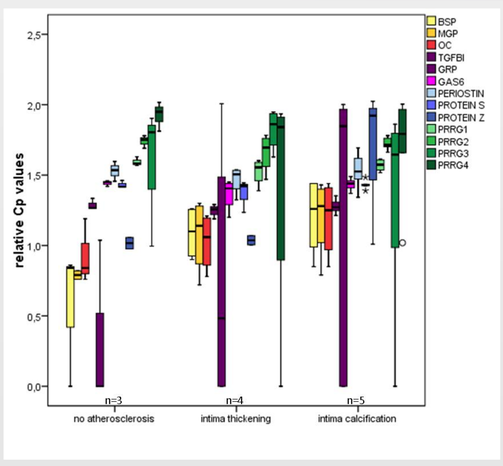

Fig.6: Gene expression of VKDPs in bone in 3 AS stages: Gene expression of VKDPs did not change during AS progression (p-values not shown).

Summary:

- We show that gene expression of classical VKDPs known to regulate bone calcification changes in the vessel wall in atherosclerosis development.
- VKDPs known to be involved in blood coagulation like protein S and Z are expressed in bone and vessels and their gene expression changes during AS progression.
- We demonstrate that different gene expression patterns exists in AS progression in bone and aorta.
- During AS progression gene expression patterns change in vessels but not in bone.
- Gene expression of VKDPs differs between bone and vessels in the stage of intima thickening but mostly in the stage of vessel calcification.

Conclusion:

Gene expression of vitamin K dependent proteins changes during calcification of the vessel wall.

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

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