Can established vascular calcification be reversed by pyrophosphate or sevelamer in an animal model of chronic renal failure?

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Background and Aim

Vascular calcification significantly contributes to the mortality in patients with chronic kidney disease (CKD). As compared to the existing treatments targeting risk factors of CKD-related vascular calcification, alternative treatment strategies directly interfering with the calcification process could open up new perspectives.

Hereto, in the current study set-up, the endogenous calcification inhibitor pyrophosphate (PPi) was studied and compared to the phosphate binder sevelamer. In previous experimental studies, both sevelamer and Ppi have proven to be effective in preventing vascular calcification in CKD, the former by controlling phosphate absorption, the latter by directly interfering with the hydroxyapatite crystal formation.

However, since most patients present with established vascular calcification, it is necessary to evaluate whether these compounds are able to slow down or even reverse this pathological mineralization process in the arteries.

Furthermore, as CKD-related bone pathology is linked to the arterial mineralization process, it is important to rule out side-effects of both compounds on physiological bone mineralization.

The current study aims to evaluate the effect of both PPI and sevelamer on the progression and/or reversibility of established vascular calcification and on bone pathology in a CKD rat model.

Materials and Methods

All rats were maintained on a protein restricted high adenine diet (0.75% adenine, 0.92% P, 1.0% Ca, 2.5% protein) for 4 weeks to induce CKD and vascular calcification. This was followed by a treatment period of 3 weeks consisting of a protein restricted adenine diet (0.075% adenine, 0.92% P, 1.0% Ca, 2.5% protein) for 4 weeks to induce CKD and vascular calcification. This was followed by a treatment period of 3 weeks consisting of sevelamer (1500 mg/kg/day via gavage), Ppi (30 µmol/kg/day or 120 µmol/kg/day via peritoneal infusion) or vehicle. A CKD control group was sacrificed before start of treatment.

Results

The adenine diet resulted in the development of severe chronic renal failure, hyperphosphatemia and hypocalemia.

Figure 2: Serum creatinine (A), serum phosphate (B) and serum calcium (C).

A tendency towards increased calcified volume in the aorta can be found for both PPI groups. Sevelamer treated animals showed no increase in calcified volume during treatment.

Figure 3: Calculated volume in the aorta measured on micro-CT scans taken before treatment (Scan 1) and after treatment (Scan 2).

Neither doses of PPI induced significant changes in bone. Sevelamer treatment resulted in an increased osteoid area which is likely due to the phosphate binding capacity seen when administering relatively high doses of phosphate binders.

Figure 4: Calcium aorta (A), calcium femoral artery (B), calcium carotid artery (C) and % calcified area on Von Kossa stained sections of the aorta (D). Lower limit of calcification: 0.5 mg/g calcium.

Figure 5: Static bone parameters. Bone area (A), osteoid area (B), osteoid perimeter (C), osteoid width (D), osteoblast perimeter (E), osteoclast perimeter (F) and eroded perimeter (G). * P<0.05 vs baseline.

Conclusions

- Pyrophosphate was not able to slow down the progression of established vascular calcification, let alone reverse the process.
- The used rat model is characterized by distinct vascular calcification due to severe CKD, which could have hindered the detection of a calcification reducing effect if one was present.
- A softer animal model for CKD characterized by less brusque and less severe vascular calcification needs to be developed.

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Poster 655

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