Background and Aim

Vascular calcification and bone pathology are two complications of chronic kidney disease (CKD) with a major impact on mortality. As vascular calcification and bone disease are both hallmarks of CKD and related to each other, a new animal model in which both pathologies can be studied concomitantly is needed, particularly to study the effect of therapeutic compounds on the evolution of arterial calcification as well as on bone metabolism. The 0.25% adenine/low vitamin K model is commonly used to study CKD related vascular calcification. However, as it shows consistent but excessive vascular calcification and chaotic and immeasurable bone mineralization due to excessive bone turnover, it is less suited to study the bone-vascular axis in one and the same animal. Moreover, with the conventional model, partial restoration of renal function after stopping adenine administration complicates evaluation of established vascular calcification in intervention studies.

This study aims to optimize a modified rat model for CKD-related vascular calcification and bone pathology which would make it feasible to evaluate treatment strategies on both arterial calcification and CKD-related vascular calcification.

Materials and Methods

Rats were maintained on a diet with low vitamin K, 1% Ca, 1% P and 6% protein with or without 0.25% adenine to induce CKD and vascular calcification.

To evaluate the onset and further progression of vascular calcification and bone disease over time, CKD rats on an adenine diet were killed at week 4, 8, 10, 11 and 12. Animals with normal renal function fed a control diet were sacrificed at week 11. Static and dynamic bone parameters were measured after double tetracycline labeling. Vascular calcification was evaluated by measurement of the arterial calcium content and histomorphometric measurement on Von Kossa stained sections. The in the abdominal aorta, the mRNA expression of proteins that play a role in cell senescence, the FGFR23-klotho axis and the Wnt signaling pathway, which are all known to be involved in arterial calcification, was studied with RT-PCR.

Based on significant univariate analysis correlations, multiple regression analysis on ranked data was performed to assess the relationship between aortic calcification and bone parameters.

Conclusions

- A low adenine / low vitamin K diet resulted in a stable CKD, moderate vascular calcification and quantifiable bone pathology after 8 weeks.
- The eroded perimeter & mineral apposition rate in the bone are major predictors for the development of vascular calcification.
- This rat model is the first one that lends itself to study these two main complications of CKD concomitantly.
- The 0.25% adenine / low vitamin K model is a valuable rat model to evaluate the effect of innovative compounds on vascular calcification and bone mineralization in CKD.

Results

1. Induction of stable severe chronic renal failure, hyperphosphatemia and hypocalcemia

2. Development of vascular calcification in the aorta and peripheral arteries

3. Development of hyperparathyroid bone disease: static bone parameters

4. Development of hyperparathyroid bone disease: dynamic bone parameters

5. Bone disturbances largely predict aortic calcification

6. Cell senescence, klotho-FGFR23 axis and osteogenesis in the aorta

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Research platform for the treatment of cardiovascular and bone diseases

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