# Vascular calcification in chronic kidney disease

# 7. SOCIETAL IMPACT

Research in the biomedicine field is meant to improve people's lives in the way of looking for new treatments and cures against different diseases, the research is focused on understanding why these diseases develop and how to stop them.

Chronic kidney disease (CKD) and cardiovascular diseases (CVD) are major causes of human deaths worldwide each year [1,2,10]. As it has been described in this thesis, CVD and CKD are very closely linked, and one is a risk factor for the other and vice versa. When a patient suffers from CKD and CVD at the same time it is called "cardio renal syndrome". This syndrome is influenced by different pathological mechanisms, and vascular calcification is one of the main mechanisms that worsens the patients' prognosis [8]. Vascular calcification is an active process highly regulated by different inducers and inhibitors, an imbalance of these regulators triggers the development of vascular calcification [53]. One of these inhibitors is vitamin K, and it is known that patients with CKD have a vitamin K deficiency [146].

Therefore, in this thesis CKD models and CKD patients were studied to unravel the reason for the vitamin K2 deficiency in CKD patients. Furthermore, this thesis focused on a new mediator of vascular calcification, finding VIF as a strong inhibitor of this pathological process.

The findings of this thesis show that in *in vivo* models of CKD, there is a decrease in the vitamin K2 concentration, the MK4 isoform, in the kidneys of CKD models compared to the control ones. MK4 is linked to the inhibition of vascular calcification by the carboxylation of vitamin K-dependent proteins [55]. Our findings should be taken into consideration in the clinical supplementation approaches for CKD patients, since a deficiency in the transport and uptake of this isoform has been described by our group [120]. The MK4 deficiency might be related to the decreased expression of HMGCR, an enzyme involved in the conversion of vitamin K1 to vitamin K2, which was observed in CKD models in this thesis. Moreover, a decreased VKORC1 and NQO1 expression, enzymes involved in the vitamin recycling cycle, has also been shown in CKD models in this thesis. The expression of the enzymes HMGCR, VKORC1 and NQO1 negatively correlates with calcium deposition in kidneys. The data in this thesis explain the increased vascular calcification found in CKD patients, due to an impairment in the vitamin K metabolism, which hinders the carboxylation of VKDP. Although differences found in CKD patients were not significant, they show a tendency similar to the CKD models, which probably will be confirmed with a higher number of samples to analyse. All these results suggest a change should be considered in the clinical supplementation strategies when vitamin K is given to CKD patients, since the incorporation and transport of vitamin K2 isoforms

is also decreased in these patients [120]. Therefore, these findings reveal a new field to improve the clinic approaches, for example using adjuvants that help the vitamin K2 transport, especially to the kidney where MK4 concentrations are decreased.

The other discovery in this thesis is the new inhibitor of vascular calcification ´VIF´. VIF has shown to have a potent inhibitory effect *in vitro*, *ex vivo* and *in vivo* in the development of vascular calcification. The results of this thesis point to VIF as a possible calcimimetic of the calcium sensing receptor (CaSR). VIF is an endogenous inhibitor of vascular calcification, that can contra-regulate it. Clinical trials to investigate a correlation between vascular calcification in CKD patients and VIF should be performed to demonstrate this in more detail. Our findings open up the field for new therapeutic approaches against vascular calcification, where no effective treatment has been found yet. More studies are needed to analyse the benefit of the use of VIF as a drug, or its small active fragment (VIF 22-28 aa). This smaller fragment has better pharmacologic properties to be produced (paper under submission), but the same potency to inhibit vascular calcification.

All these novel findings have been presented and discussed in different international conferences and meetings, through posters and oral presentations. Furthermore, data from the first part of this thesis have been published in a peer-reviewed journal.