

# Identification and characterization of the mediators of the calcification paradox

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## 7. SOCIETAL IMPACT

Research is the search for facts and knowledge, which not only develops our critical thinking but also improves our day to day life. The prevalence and incidence of cardio-renal syndrome have been increasing worldwide. The high mortality and morbidity of these diseases highlight the need of investigating the underlying causes and consequences. Research in the cardiovascular field is ever-expanding; however, there is a pressing need to provide companies, health care professionals and the general public with the latest basic research from labs in a form that can be implemented.

This thesis is focused on gaining insights into vascular calcification processes and accompanied consequences such as osteoporosis, that contribute to cardiovascular mortality. We describe CRS, CKD and CVD, highlighting the impact of vascular calcification in each of these diseases. In addition, we describe the lowering of bone mineral density in CKD and CVD, a cause and consequence of vascular calcification. Hence, this thesis elucidates the prevalence of various consequent disorders in an individual as a by-product of chronic diseases such as CRS. This in turn highlights the need for translational research that focuses on personalised treatment, without focusing on the treatment of a single disease.

Further, we characterize CBF as a novel inhibitor of VC originating from the adrenal gland protein Chromogranin A. CBF concentration reduces in ESRD patients who are predisposed to VC, indicating the role of this peptide in preventing VC. We illustrate the mechanism by which CBF is released from its parent peptide and by which it reduces VC. The understanding of these mechanisms opens up new avenues for the treatment of VC and for investigating the causes of VC in these patients. This also indicates that a higher reduction in cardiovascular morbidity can be achieved by understanding the role of different mediators of VC and implementing this knowledge.

In addition, we identified and characterized a novel mediator of the calcification paradox, CBF (1-8) which reduces medial VC more efficiently as compared to its parent peptide CBF. We show that CBF (1-8) reduces VC by reducing the transdifferentiation of SMCs by reducing the expression of osteogenic genes. Additionally, CBF (1-8) reduces the loss in bone mineral density *in vivo* under calcification inducing conditions. Identification and characterization of mediators of the calcification paradox open up new avenues to prevent and treat vascular calcification and osteoporosis at the same time, reducing the strain on healthcare facilities caused by CVD and CKD.

**The findings from this thesis present three potential clinical applications of CBF and CBF (1-8).** Firstly, either can be used as a therapy for VC in CVD and CKD patients or patients undergoing dialysis who are predisposed to losing small peptides during this process. Secondly, the release of CBF can be enhanced for therapeutic purposes by targeting the release of CBF from its parent peptide. Lastly, in patients predisposed to osteoporosis CBF (1-8) can potentially overcome low bone density. Also, it highlights the need to investigate and improve processes such as dialysis to replenish the loss of metabolites and peptides lost during the removal of toxins.

These findings open new options for the treatment of VC without impairing mineralization in bones. This thesis provides the first direct peptidic link between VC and bone mineralization disease which has great clinical implications. These findings need to be tested in human trials to help reduce cardiovascular mortality and morbidity.

Many efforts have been made to make the research presented in this thesis available to the public by publications in peer-reviewed journals, poster presentations and oral presentations both for the scientific community and the public.