

Chasing the perfect storm

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Appendix

Social and scientific impact



Age-related diseases, including cardiovascular diseases (CVD), chronic kidney disease (CKD) and vascular calcification (VC) are on the rise globally. VC is of particular interest because it is related to, as well as can cause multiple complications such as heart failure and high blood pressure. In CKD, kidneys fail to excrete waste products from the blood, thereby accumulating them in the blood. The waste products are then referred to as uremic retention molecules (URM). These URM strongly contribute to increased VC, CVD, and mortality in CKD patients. Ceasing health comes with a heavy burden on quality of life and rapidly increasing health care cost. Furthermore, multi-morbidity tends to accumulate within an individual with age, and with the global population aging, over-all disease burden is rising.

This thesis aims to identify risk factors contributing to increased CVD burden, with a focus on CKD related contributors, since CKD is considered a disease of accelerated ageing. Further we investigated methods to detect individuals which potentially are at high risk to develop CVD, and we investigate how to cost effectively provide save therapy for prevention and treatment of CVD.

In chapter 2 of this thesis, we describe the development of a novel test to detect the propensity of human serum to induce calcification by using cells from the vasculature and termed this assay BioHybrid. We showed that the BioHybrid detects the anticipated reaction to sera from patients, by showing more calcification with sera from people suffering from a range of VC related diseases. The advantage of the BioHybrid over previously available biomarker assays is, that it needs less serum to test the calcification reaction over time, and it is more reliable in its readout. Another perk of this test is, it considers all serum components and not just one single biomarker. In chapter 3 we describe how the test is further developed, using vascular cells derived from induced pluripotent stem cells (iPSCs). This allows to provide an endless source of similar vascular cells, allowing for more standardisation and distribution of the BioHybrid. Additionally, using iPSC derived vascular cells makes the BioHybrid more precise and increases repeatability. Furthermore, we applied the BioHybrid to serum samples of patients with established and proven coronary artery calcification. Next, we used these results as well as other clinical data to predict progression of VC. We showed that the BioHybrid contributes substantially to identification of high-risk patients. Another advantage of the BioHybrid lays in its simplicity. It can potentially be used in middle- and low-income countries, with common laboratory equipment, and it can strongly contribute to the identification of high-risk patients, enabling early treatment thereby preventing future health care cost and disease burden. The BioHybrid could be used commercially and may have a future in routine clinical practice, with specific applications in personalized medicine.

In chapter 4 we provide an extensive review and summary of the literature on URM and VC. Currently, only few URM are researched with respect to their relation to VC. We point out gaps in existing research, paving the way for a better understanding of this subject. We also provide a roadmap for systematic assessment of URM to effectively allow fact-based decision making. In the subsequent chapter, we utilize this information, and create a list, ranking URM by likelihood of being pro-calcific. We tested the top 4 candidates, yet the list may serve for informed future decision making. Of the tested 4 candidates, 2 are newly identified molecules being pro-calcific. Para-cresyl sulfate

(pCS), being among the most recognized URM. We showed that vitamin K directly counteracts the detrimental effects of pCS and investigated the molecular mechanism behind it. Understanding how pCS and other URM contribute to VC, allows to better understand the process of VC in CKD providing the basis for development of targeted therapies.

In chapter 6, we provide an assessment of vitamin K status in patients with high cardiovascular risk, using two different vitamin K dependent surrogate markers. Four different patient groups were included: 2 dialysis dependent and 2 non-dialysis dependent patient groups. We observed normal vitamin K status in non-dialysis patients and especially compromised vascular vitamin K stores in dialysis, likely rendering these patients susceptible to accelerated VC. Both surrogate markers correlated poorly with each other, highlighting the importance of which marker is chosen. Our findings may aid physicians in their analytical and therapeutical decision making, and in finding optimal treatment strategies.

The results of this PhD project are published in various open-access scientific journals (complete list in subsequent chapter) and more research is in preparation for publication. All published articles combined have been read more than 9609 times and been cited over 28 times, underscoring the relevance of this research for the scientific community. We encourage scientists to use the BioHybrid, by publishing our detailed, video supported, protocols. Furthermore, the results of this work have been presented at international conferences, thereby exchanging knowledge, creating discussion, and sparking new ideas among researchers.

Importantly, and in light of the recent COVID-19 pandemic, the discussion around the impact of scientific evidence in public decision making intensified. Also, outreach and dissemination of results by researchers has received more attention and gained importance. Given the funding from public resources, research should benefit the public, but also reach the general population to increase understanding, acceptance, and support. To raise awareness, we shared the scientific background and novel findings of this thesis via various ways, including distribution on several social media platforms, development of flyers for patients distributed at the hospital, a podcast explaining the project in layman's terms and training of students.

In its essence, research conducted in this PhD project aims to reduce the disease burden coming with an ageing population, one of the major challenges for mankind in this century. We worked on a low cost, easy to implement, reproducible test to aid risk assessment for VC, a major contributor to CVD. Even in the COVID-19 pandemic, CVD is still the number one cause of premature death globally. We provided a framework for researchers to build on for URM research and started to fill-in knowledge gaps. Lastly, we contributed to the growing body of knowledge supporting vitamin K as a potent, cost effective and safe way of treating and preventing CVD.