Sodium [18f]fluoride positron emission tomography for non-invasive identification of micro-calcifications as marker of atherosclerotic plaque vulnerability

Valorisation

According to the most recent data of the World health organisation (*i.e.*, WHO), cardiovascular disease (CVDs) is the leading cause of death globally. An estimated 17.9 million people died from CVDs in 2019, representing 32% of all global deaths; as a comparison, in 2020 all types of cancer combined accounted for nearly 10 million deaths. Out of the 17 million premature deaths (*i.e.*, under the age of 70) due to non-communicable diseases in 2019, 38% were caused by CVD (World Health Organization, 2021).

Almost 90% of CVDs are caused by the formation of atherosclerotic plaques (Planer et al., 2014), which may become vulnerable, thus having an increased risk of rupture. If one of these plaques rupture, it becomes complicated and forms a blood clot, which lead to tissue ischemia either at the site of the plaque (*e.g.*, myocardial infarction, peripheral artery disease) or at another site *via* embolism (*e.g.*, stroke). Almost 85% of CVD deaths are due to one of these two mechanisms. Inflammation and micro-calcification are established hallmarks of vulnerable atherosclerotic plaque development; therefore, the identification and the subsequent early on treatment of these processes would help ease the burden and load CVD have on the medical system and society as a whole.

The aim of this thesis was twofold: (1) to try to assess novel methods for early identification of micro-calcification and later also of inflammation and (2) to test the feasibility of combating micro-calcification with vitamin K.

The knowledge gained from the experiments performed here are of general interest for every single one of us, as, because of our western diet, we all shall develop atherosclerotic plaques at some point. Detecting vulnerable plaques would first enable invasive resection therapy (*i.e.*, endarterectomy) to be directed against plaques, which may cause harm, instead of only resecting plaques, which cause a certain lumen reduction. Moreover, the findings form the vitamin K efficiency, if also reflected in humans as in mice, would help reduce the overall number of premature deaths and of deaths caused by CVD. The early detection and the subsequent treatment of atherosclerosis suggested by this thesis would prove to be an exceptional gain in human life and realising the burden of cardiovascular disease on healthcare in general.

These results of this thesis may also be of interest for several targeted groups. First, clinicians involved in the patient care may take advantage of these findings. Currently, there is no effective way to detect vulnerable plaques; they are identified with the help of

several imagistic methods, which are all based more or less on determining the degree of luminal stenosis the plaque causes on the artery. However, this is rather a poor indicator, because, as shown in Chapters I and II, plaque size is not a vulnerability feature. The promise of the two imaging techniques assessed in Chapters III and V, is to improve patient stratification, by identifying patients at risk. This would mean that the treatment and its intensity may be tailored for each patient around the degree of vulnerability of the plaques developed. This would also improve the healthcare of patient with asymptomatic CVD, as they rarely receive any treatment, only before it's too late. Second, an important target group would be the food industry and healthcare departments. As show in Chapter II and tested in Chapter III, vitamin K seems to protect against the development of micro-calcification (*i.e.*, a known marker for vulnerability); therefore, increasing the daily recommended dose or providing specific vitamin K2 (*i.e.*, more exactly MK-7) supplements in a high enough dose, would help combat micro-calcification and therefore vulnerable plaque formation at the level of general population. Here it is also worth mentioning that there is no evidence for overdose of vitamin K and also no risk associated with increasing the recommended dose for this specific type of vitamin.

The ultimate goal of this project and therefore also of this thesis was set to improve knowledge on micro-calcification and inflammation during atherosclerotic plaque development and to investigate how vitamin K influences this process. The generated data was presented at national and international conferences and published in peer-reviewed open access journals. At the end of the project, we have shown the potential of two tracers to reliably detect micro-calcification and inflammation respectively, and that vitamin K holds the potential to inhibit vascular micro-calcification within the atherosclerotic plaque. This research will serve as a steppingstone for further and more accurate detection of vulnerable plaque features and for a better treatment and prevention of CVD.