

Vitamin K is a group of fat-soluble vitamin involved in the regulation of coagulation and bone and calcium homeostasis via vitamin K-dependent (VKD) proteins. Recent epidemiological evidence suggest that intake of vitamin K2 (exerting mainly extrahepatic activity), but not vitamin K1 (exerting mainly hepatic activity) reduce cardiovascular and total mortality. This effect cannot be explained by profile of of action of vitamin K2 described so far. Based on these unpublished results we claim that impairment of endogenous synthesis of vitamin K2 in endothelium contribute to the development of endothelial dysfunction in atherosclerosis and supplementation with vitamin K2 reverse the endogenous deficit of vitamin K2 in the endothelium with subsequent improvement of carboxylation status in endothelium and endothelial function. Altogether, our preliminary results suggest that vitamin K2 plays an important role in the regulation of endothelial function that has been not revealed so far.

Surprisingly, despite long-term history of vitamin K research, knowledge on the role of vitamin K in the regulation of endothelium in the context of physiology, biochemistry, pathophysiology and pharmacology of endothelium and various diseases related to endothelial dysfunction is virtually absent. To complement this knowledge within the project, it may bring not only a new understanding of the mechanisms of exogenous vitamin K2, and regulation of endothelium by this vitamin, but also possibly open new therapeutic avenues for many diseases associated with vascular endothelial dysfunction.

In this project we will use E3L.CETP mice representing a clinically-relevant and unique model of slowly progressing endothelial dysfunction induced by mild hyperlipoproteinaemia preceding atherosclerosis development. The better understanding of the mechanisms of endothelial dysfunction in this model may foster mechanistic studies on novel pharmacotherapeutic mechanisms of endothelial dysfunction *in vivo*.