Factors associated with a modulation of fibrin clot structure and resistance to fibrinolysis in patients with protein C and protein S deficiency

Protein C (PC) and Protein S (PS) are key players in the human natural anticoagulant system, to maintain a balance between blood clot formation and breakdown. PC is activated by thrombin in the presence of thrombomodulin (TM). Once activated, PC helps deactivate two crucial clotting factors, factor V (FV) and FVIII, which are necessary for stable clot formation. PS enhances the effectiveness of activated PC, amplifying its anticoagulant effects. Together, they ensure efficient and precise clot regulation. When PC or PS levels are reduced, the risk of thrombosis is up to 10 times higher than in healthy individuals.

Our study explores how deficiencies in PC or PS affect clot structure and function. We also aim to identify factors in the blood that might influence these changes. Using advanced laboratory techniques and proteomic analysis this project will show whether deficiencies in PC or PS might make clots more prothrombotic and examine possible ways to counteract these effects.

This study will enroll 100 adult patients of both sexes with inherited mild-to-severe type I and II PC or PS deficiencies - characterized by PC/PS activity or activity and antigen levels below 70% - to investigate their prothrombotic tendencies. Heathy volunteers (n=50) will serve as controls. Comprehensive assessment of thrombophilic factors, along with FXIII levels, endogenous thrombin potential, and thromboelastographic variables will be conducted. Fibrin clot properties, including clot permeation and fibrinolysis, whole blood clot contraction, and viscoelastic clot properties will be assessed. High-resolution imaging techniques like scanning electron microscopy together with confocal and fluorescence microscopy will offer detailed insights. Additionally, mechanistic experiments, proteomic analyses, and *in vitro* studies of PC/PS oxidation, glycation, and plasma spiking will explore the impact of post-translational modifications on clot structure and function.

This project addresses a critical gap in understanding the prothrombotic risks associated with natural anticoagulant deficiencies. Associations between PC or PS deficiency and a prothrombotic fibrin clot phenotype remains unexplored. This project aims to reveal the underlying mechanisms of these tendencies and assess whether they can be mitigated by PC or PS replacement, which may have potential clinical implications.