Thesis for the Degree of Doctor of Philosophy (Ph.D.)

FXIII ACTIVITY, ANTIGEN LEVEL AND FXIII-A VAL34LEU POLYMORPHISM IN CORONARY ARTERY DISEASE

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Blood coagulation factor XIII (FXIII) is a zymogen (protransglutaminase) of tetrameric structure (A_2B_2). Thrombin removes an activation peptide of 37 amino acid residues from FXIII-A, then in the presence of Ca^{2+} the carrier/inhibitory FXIII-B dissociate and FXIII-A assumes an enzymatically active configuration. The main function of FXIII in normal hemostasis is to cross-link fibrin chains and to attach proteins important in the regulation of fibrinolysis to the fibrin network. Among FXIII-A gene polymorphisms Val34Leu polymorphism is the most well-characterized because of its suspected thrombo-protective effect.

The association between FXIII levels and coronary sclerosis (CS) and myocardial infarction (MI) was investigated using adequate laboratory methods. The effect of elevated FXIII levels and FXIII-A Val34Leu polymorphism on the risk of CS/MI was also examined.

The presence of FXIII-A Leu34 allele or homozygous Leu34 genotype alone did not change the risk of CS/MI in the Hungarian population. However, when patients with elevated fibrinogen level were separately investigated, the Leu34 allele provided a statistically significant protection against MI. Fibrinogen concentration modulates the effect of Leu34 allele on the risk of MI, its protective effect emerges at increasing fibrinogen concentration.

The general protective effect of FXIII-A Leu34 allele against coronary artery disease in the Caucasian population was demonstrated by a meta-analysis of 16 studies. However, it was also indicated that the prevalence of this effect depends on environmental factors and gene-gene interactions.

We first described in the literature that elevated FXIII level was an independent risk factor for MI in females and suggested that FXIII determination is to be included in the gender-specific risk profile.

We demonstrated that in patients with CS and MI FXIII-A Val34Leu polymorphism influences plasma FXIII levels. In MI+ patients homozygous for the Leu34 allele FXIII levels were significantly lower than in heterozygous and wild type patients. The specific activity of FXIII was independent of FXIII-A Val34Leu polymorphism. It is presumed that in MI+ Leu34 homozygous patients faster activation of Leu34 FXIII is combined with a higher extent of low-scale thrombin formation, more FXIIIa is formed which is then eliminated from the circulation resulting in lower FXIII levels.