Elevated plasma factor XI is predicts cardiovascular complications in patients with type 2 diabetes mellitus

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Funding Acknowledgements: Type of funding sources: Public Institution(s). Main funding source(s): Jagiellonian University Medical College

Background: Atherothrombotic complications are common in patients with type 2 diabetes mellitus (T2DM), reflecting a chronic prothrombotic state. Circulating factor XI (FXI) has been associated with a prothrombotic fibrin clot phenotype and predicted myocardial infarction, stroke and cardiovascular (CV) death in a number of diseases, including CAD. Its role in T2DM is largely unknown.

Purpose: The purpose of this study was to assess plasma FXI as a predictor of atherothrombotic events in T2DM patients. We also aimed to establish the determinants of elevated plasma FXI in this group of patients.

Methods: In a cohort of 156 patients aged 43–83 years, 56% male, with T2DM of a median duration time of five years, 64.7% with diagnosed CAD, we measured FXI along with a number of fibrin clot parameters, including turbidity, permeation, compaction, lysability, maximum concentration of D-dimer (D-D max), and rate of D-dimer release during tissue plasminogen activator-induced clot lysis. Patients were followed for a median time of 72 (68-74) months for a composite endpoint of nonfatal myocardial infarction (MI), nonfatal stroke, and cardiovascular (CV) death.

Results: Follow-up was complete for 133 (85.3%) patients. There were 21 (16%) cases of the composite endpoint, including one nonfatal MI, four nonfatal strokes and 16 cases of CV death. Patients with and without the composite endpoint shared a similar demographic and clinical profile with the exception of age and white blood cell count – patients with the endpoint were older (69.4 [8.4] vs. 65.4 [7.8] years, p=0.03) and had a higher leukocyte count (7.8 [1.9] vs. 7.0 [1.3], p=0.02) as compared with the remainder. FXI was elevated above the upper limit of 120% in 25 (18.8%) patients, including 16 (61.9%) with the composite endpoint vs. 12 (10.7%) without the composite endpoint, p<0.001. Individuals with the composite endpoint had higher baseline FXI concentrations as compared with the remainder (120.1 ± 16.8 vs. 104.9 ± 10.7%, p < 0.001), along with higher D-D max (4.1 [3.8-4.3] vs. 3.8 [3.6-4.1] mg/l, p = 0.006) and slightly longer lysis time (t50% 10.1 [9.8-10.9] vs. 9.8 [8.9-10.4] min, p = 0.03). On multivariable analysis, co-existing CAD, LDL cholesterol, and thrombin activatable fibrinolysis inhibitor activity were independent predictors of elevated FXI in T2DM patients.

Conclusion: Elevated plasma FXI in T2DM patients is associated with CAD, LDL cholesterol and TAFI, and predicts myocardial infarction, stroke, and CV death in long term follow-up. Our finding may have implications for risk stratification and suggests a role for FXI inhibitors in T2DM patients with a high risk of atherothrombotic complications.