Prothrombotic phenotype of type-2 diabetes mellitus patients with stable angina: focus on platelet Tissue Factor

L. Rossetti[1], M. Brambilla[1], P. Canzano[1], M. Mapelli[1], D. Trabattoni[1], A. Lualdi[1], E. Tremoli[1,2], M. Camera[1,2]

[1]Centro Cardiologico Monzino IRCCS
[2]Dept. of Pharmacological and Biomolecular Sciences, Università degli Studi di Milano, Milan, Italy

Background- Despite low-dose aspirin therapy as primary prevention, patients with type-2 diabetes mellitus ($T2DM^+$) have enhanced platelet reactivity and a hypercoagulable state, supporting the evidence of a greater incidence of coronary artery disease (CAD) compared to patients without diabetes ($T2DM^-$). Tissue Factor (TF), the main activator of blood coagulation, is expressed also by platelets. We previously showed that platelet TF (pTF) is significantly increased in CAD patients compared to healthy subjects (HS). No previous study has assessed whether T2DM may influence pTF thus potentially contributing to the higher thrombogenicity observed in CAD patients with T2DM.
Aim- The objective of the study is to provide insight into the enhanced risk of thrombotic complications associated with T2DM assessing pTF expression and the overall prothrombotic potential in stable angina (SA^+) patients with T2DM compared to those without T2DM.
Methods- We enrolled 85 SA^+ patients, 32 $T2DM^+$ and 53 $T2DM^-$, 28 SA^- $T2DM^+$ patients and 37 HS. All patients were treated with 100 mg/die aspirin. Assessment of surface and intracytoplasmic pTF expression was performed by whole blood flow cytometry; the prothrombotic potential was analyzed by thrombin generation assay (CAT) in isolated platelets using Thrombinoscope and the global haemostatic function was evaluated by thromboelastometry (Rotem).
Results- In SA+T2DM+ patients the number of circulating platelets expressing on their surface TF is double the amount observed in SA+T2DM- patients and in HS ($p<0.05$). When the expression of TF was assessed intracellularly, the number of TF+ platelets was again significantly higher in SA+T2DM+ compared to SA+T2DM- patients (27.53±2.8 vs. 14.98±1,34, $p<0,001$). This resulted in an increased thrombin generation capacity of platelets from SA^+ $T2DM^+$ patients, being shorter both the lag time and the time to peak. Treatment of samples with an anti-TF antibody in order to assess TF contribution to thrombin generation resulted in an increase in the time needed to start thrombin generation in both groups of patients and the delay was significantly greater in T2DM patients. Maximum Clot Firmness, α-Angle and Maximum Velocity of clot formation assessed by ROTEM were all significantly increased in SA^+ $T2DM^+$ patients.
Conclusion- The present study sheds new light on the mechanisms involved in the enhanced prothrombotic phenotype ofSA patients with T2DM showing that, despite aspirin treatment, the number of TF+ platelets is significantly higher in SA+T2DM+ compared to SA+T2DM- patients. This results in a higher TF-dependent thrombin generation capacity of platelets from SA+T2DM+ patients compared to SA+T2DM- patients.