OVEREXPRESSION OF PLATELET AND MONOCYTE CYCLOOXYGENASE-2 IN CORONARY THROMBI FROM DIABETIC PATIENTS: A POTENTIAL MECHANISM OF ASPIRIN TREATMENT FAILURE

Annalisa Iezzi MD, Maria Luigia Fazia PhD, Chiara Cuccurullo MD, Carlo Corona PhD, Carlo Patrono MD, Franco Cuccurullo MD, Andrea Mezzetti MD, Francesco Cipollone MD

Atherosclerosis, Hypertension and Dyslipidemia Unit, "G. d'Annunzio" University of Chieti-Pescara, and Center for Aging Sciences, "G. d'Annunzio" University Foundation, Chieti, Italy

Background Everyday clinical practice shows that antiplatelet therapy may not always be efficient enough in diabetics. Although the concept of aspirin resistance is extensively studied, its precise mechanisms are still largely unknown. We tested the hypothesis that the expression of cyclooxygenase (COX)-2 in newly formed platelets (PLTs) and monocytes might represent a mechanism of aspirin-insensitive PLT activation in diabetic patients.
Methods We studied 25 type II diabetic patients (T2D) and 25 matched non diabetic patients developing acute myocardial infarction (AMI). Ten type I diabetic (T1D) patients with AMI were also studied to investigate the role of insulin in PLT function. All patients underwent immediate thrombectomy before PTCA, and coronary thrombi were collected and analyzed by immunohistochemistry. We also measured mean PLT volume (MPV), and COX-2 expression in circulating PLTs and monocytes.
Results COX-2 expression in coronary thrombi was significantly higher in the diabetic patients vs controls (18±4% vs 3±1.2%, $P<0.001$), with similar rates in T1D (17±6%), and T2D (16±4%). COX-2 staining indicated its localization in PLTs and monocytes. COX-2 co-localized with thromboxane-synthase, type 1 inducible prostaglandin E-synthase, and EP3 receptor. Higher COX-2 expression in thrombi from diabetic patients was associated with a comparably higher COX-2 expression in circulating PLTs and monocytes (12±1% vs 2.5±0.3%, and 16±2.1% vs 3±1.3%, respectively $P<0.001$), mainly when present as PLT-monocyte microaggregates (80±6% vs 20±3% for PLTs, and 74±4% vs 14±3% for monocytes, respectively; $P<0.001$). Enhanced COX-2 in PLTs likely reflected an accelerated PLT turnover in diabetic patients, because it was associated with higher serum level of thrombopoietin (68.2±26 vs 22.3±14 pg/mL, $P<0.001$) and higher MPV (12.4±2.3 vs 8.4±1.5 fl, $P<0.001$). Notably, a strong correlation between HbA1c, MPV and COX-2 expression was found in diabetics, thus suggesting that PLT turnover may be regulated by glycemic control.
Conclusions Newly formed, COX-2 expressing PLTs as well as PLT-primed monocytes characterize coronary thrombi of diabetic patients developing myocardial infarction. Aspirin-resistant thromboxane biosynthesis is likely to contribute to coronary occlusion and could account, at least in part, for treatment failure in diabetes.