

PIASTRINE: ALTERAZIONI QUALITATIVE O QUANTITATIVE

OXIDATIVE STRESS-RELATED PLATELET HO-1 AND MICRORNA MODULATION IN PATIENTS WITH TYPE 2 DIABETES MELLITUS UNDER ASPIRIN THERAPY

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Background and Aims. Patients with type 2 diabetes mellitus (T2D) exhibit enhanced platelet reactivity and an increased risk of atherothrombotic events. Although low-dose acetylsalicylic acid (ASA) irreversibly inhibits cyclooxygenase-1, a substantial proportion of patients with T2D show a suboptimal antiplatelet response. Oxidative stress has been proposed as a key mechanism underlying this variability. The aim of this study was to investigate the relationship between oxidative stress-related pathways, platelet function, and ASA responsiveness in patients with T2D, focusing on platelet heme oxygenase-1 (HO-1) and platelet-associated microRNAs (miRNAs).

Methods. Patients with T2D receiving chronic ASA therapy (T2D+ASA, n = 55), patients with T2D not receiving ASA (T2D, n = 11), and subjects without T2D (NOT2D, n = 20) were enrolled. Chronic ASA therapy consisted of 100 mg/day for at least one month. Blood and urine samples were collected for platelet isolation and biochemical analyses. Patients in the T2D+ASA group were stratified into tertiles according to platelet HO-1 levels Figure 1A. Platelet miRNA expression profiles were identified by next-generation sequencing and validated by real-time PCR. KEGG pathway enrichment analysis was performed on differentially expressed platelet-associated miRNAs.

Results. Platelet HO-1 levels differed significantly among groups. Patients with T2D, regardless of ASA treatment, exhibited significantly lower platelet HO-1 levels compared with NOT2D subjects (both $P < 0.001$), Figure 1B. Among T2D+ASA patients, lower platelet HO-1 levels were associated with higher levels of markers of platelet activation, including serum thromboxane B₂ (first vs third tertile, $P = 0.036$) and urinary 11-dehydro-thromboxane B₂ ($P = 0.030$), Figure 1C-D. A total of 62 platelet-associated miRNAs were identified. Reduced expression of hsa-let-7b-5p, hsa-miR-98-5p, hsa-miR-423-5p, hsa-miR-652-3p and hsa-miR-625-5p, and increased expression of hsa-miR-21-5p, hsa-miR-23a-3p, hsa-miR-126-5p, hsa-miR-150-5p, hsa-miR-151a-3p and hsa-miR-200c-3p were observed in patients with lower HO-1 levels, Figure 1E-F. KEGG analysis revealed enrichment of pathways related to platelet activation, fluid shear stress and atherosclerosis.

Conclusions. Patients with T2D exhibit reduced platelet HO-1 levels independently of chronic low-dose ASA therapy, indicating a persistent impairment of platelet antioxidant capacity that may contribute to enhanced platelet reactivity and reduced responsiveness to antiplatelet treatment. In this clinical context, lower HO-1 levels are associated with a reduced expression of regulatory let-7 family members, including hsa-let-7b-5p and hsa-miR-98-5p, suggesting a failure of compensatory mechanisms linking platelet miRNAs to redox-sensitive pathways, potentially due to insufficient repression of the HMOX1 transcriptional inhibitor Bach1. Consistently, platelet-associated miRNA profiling and KEGG pathway analysis indicate that low HO-1 levels are associated with a less adaptive modulation of platelet activation and platelet-vascular signaling pathways, which may translate into suboptimal antiplatelet responses and an increased risk of atherothrombotic events.

