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## Transferrin Saturation and Its Association with Platelet Reactivity

Isabella Russo, Cristina Barale, Franca Napoli, Marco De Gobbi, Angelo Guerrasio and Alessandro Morotti

### Introduction.

While a plethora of risk factors have been well established as predictors for atherosclerosis and coronary heart disease, the possible association between body iron status and the risk of cardiovascular disease has yielded conflicting results. Epidemiological studies have found a significant negative association of transferrin saturation and coronary heart disease or myocardial infarction suggesting that higher body iron stores possibly confer a protective effect towards developing cardiovascular diseases. Despite the pivotal role of platelets on the pathogenesis of thrombotic complications, little information is available about the relationships between transferrin saturation and platelet reactivity. Aim of this study was to evaluate the influence of transferrin saturation on platelet function.

### Methods.

The study included two groups: 32 healthy volunteers (17M/15F, age: 55±5 years) and 45 hereditary hemochromatosis (HH) patients (34M/11F, age: 62±2 years). HH patients were characterized by high prevalence of C282Y and/or H63D mutations of the hemochromatosis gene (HFE) and showed, just before the last therapeutic bloodletting, serum transferrin saturation and ferritin levels of 51±4% and 176±34 ng/ml, respectively.

In platelet samples from healthy subjects and HH patients, we evaluated the effects of a 15-min preincubation with holotransferrin (holoTf) or apotransferrin (apoTf) (10-80 nmol/l) on: i) maximal aggregation to ADP (10 µmol/l), collagen (4 mg/l), epinephrine (5 µmol/l) and arachidonic acid (AA) (1 µmol/l) (Born's method); ii) expression of platelet activation marker CD62P in response to collagen (4mg/l) (flow-cytometry); iii) activation of signaling pathways PI-3K/Akt and MAPK/Erk-1/2 in response to collagen (4mg/l) and AA (100 µmol/l) (Western Blot); iv) reactive oxygen species (ROS) stimulated by AA (100 µmol/l) (DCF-DA fluorescence).

### Results.

In healthy subjects we found that platelet exposure to holoTf, but not apoTf, significantly decreased platelet reactivity. In particular, 40 µmol/l HoloTf: i) reduced maximal aggregation by 39±1% to ADP, 40±4% to collagen, 49±3% to epinephrine, and 48±4% to AA (versus each agonist alone:  $p<0.05$ ); ii) reduced platelet membrane expression of CD62P by 50±3% to collagen ( $p<0.0001$ ); iii) reduced pAkt levels by 40±5% with collagen ( $p<0.001$ ), and 38±2% with AA ( $p<0.0001$ ); reduced pErk-2 levels by 66±5% with collagen ( $p<0.0001$ ), and 38±4% with AA ( $p<0.005$ ); iv) reduced the AA-induced ROS production by 35±3% ( $p<0.001$ ). Also in platelets from HH patients holoTf significantly attenuated platelet reactivity. In fact, 40 µmol/l HoloTf: i) reduced platelet aggregation by 45±4% to ADP, 38±9% to collagen, 57±4% to epinephrine, and 49±5% to AA (versus each agonist alone:  $p<0.05$ ); ii) reduced platelet membrane expression of CD62P by 54±6% to collagen ( $p<0.0001$ ); iii) reduced pAkt levels by 37±6% with collagen ( $p<0.005$ ), and 41±7% with AA ( $p<0.0001$ ); reduced pErk-2 levels by 59±7% with collagen ( $p<0.0001$ ), and 42±5% with AA ( $p<0.005$ ); iv) reduced the AA-induced ROS production by 37±5% ( $p<0.001$ ). The levels of transferrin saturation, but not of ferritin, were inversely correlated with the main platelet reactivity parameters; in particular, we found negative and significant correlations with the maximal aggregation to ADP ( $r=-0.332$ ,  $p=0.05$ ), collagen ( $r=-0.511$ ,  $p=0.002$ ), epinephrine ( $r=-0.404$ ,  $p=0.02$ ), AA ( $r=-0.460$ ,  $p=0.009$ ) and the CD62P expression at both basal conditions ( $r=-0.456$ ,  $p=0.02$ ) and after stimulation with collagen ( $r=-0.459$ ,  $p=0.05$ ) or AA ( $r=-0.629$ ,  $p=0.001$ ).

### Conclusions.

In healthy subjects, platelet exposure to holoTf, but not apoTf, reduced platelet reactivity as showed by a significant decrease of: i) aggregation, ii) membrane expression of CD62P, iii) activation of PI3K and MAPK pathways, and iv) oxidative stress. The effects of holoTf on platelet response were preserved in HH patients where transferrin saturation levels inversely correlated with platelet aggregation and activation. These results induce to hypothesize that in the association of high transferrin saturations and lower risk of cardiovascular diseases a role could be exerted by transferrin saturation effects on platelets.

Disclosures No relevant conflicts of interest to declare.

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