

## Depletion of HDL3 high density lipoprotein and altered functionality of HDL2 in blood from sickle cell patients.

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### Abstract

In sickle cell disease (SCD), alterations of cholesterol metabolism is in part related to abnormal levels and activity of plasma proteins such as lecithin cholesterol acyltransferase (LCAT), and apolipoprotein A-I (ApoA-I). In addition, the size distribution of ApoA-I high density lipoproteins (HDL) differs from normal blood. The ratio of the amount of HDL<sub>2</sub> particle relative to the smaller higher density pre- $\beta$  HDL (HDL<sub>3</sub>) particle was shifted toward HDL<sub>2</sub>. This lipoprotein imbalance is exacerbated during acute vaso-occlusive episodes (VOE) as the relative levels of HDL<sub>3</sub> decrease. HDL<sub>3</sub> deficiency in SCD plasma was found to relate to a slower ApoA-I exchange rate, which suggests an impaired ABCA1-mediated cholesterol efflux in SCD. HDL<sub>2</sub> isolated from SCD plasma displayed an antioxidant capacity normally associated with HDL<sub>3</sub>, providing evidence for a change in function of HDL<sub>2</sub> in SCD as compared to HDL<sub>2</sub> in normal plasma. Although SCD plasma is depleted in HDL<sub>3</sub>, this altered capacity of HDL<sub>2</sub> could account for the lack of difference in pro-inflammatory HDL levels in SCD as compared to normal. Exposure of human umbilical vein endothelial cells to HDL<sub>2</sub> isolated from SCD plasma resulted in higher mRNA levels of the acute phase protein long pentraxin 3 (PTX3) as compared to incubation with HDL<sub>2</sub> from control plasma. Addition of the heme-scavenger hemopexin protein prevented increased expression of PTX3 in sickle HDL<sub>2</sub>-treated cells. These findings suggest that ApoA-I lipoprotein composition and functions are altered in SCD plasma, and that whole blood transfusion may be considered as a blood replacement therapy in SCD. Impact statement Our study adds to the growing evidence that the dysfunctional red blood cell (RBC) in sickle cell disease (SCD) affects the plasma environment, which contributes significantly in the vasculopathy that defines the disease. Remodeling of anti-inflammatory high density lipoprotein (HDL) to pro-inflammatory entities can occur during the acute phase response. SCD plasma is depleted of the pre- $\beta$  particle (HDL<sub>3</sub>), which is essential for stimulation of reverse cholesterol from macrophages, and the function of the larger HDL<sub>2</sub> particle is altered. These dysfunctions are exacerbated during vaso-occlusive episodes. Interaction of lipoproteins with endothelium increases formation of inflammatory mediators, a process

counteracted by the heme-scavenger hemopexin. This links hemolysis to lipoprotein-mediated inflammation in SCD, and hemopexin treatment could be considered. The use of RBC concentrates in transfusion therapy of SCD patients underestimates the importance of the dysfunctional plasma compartment, and transfusion of whole blood or plasma may be warranted.

**KEYWORDS:** Inflammation; acute phase proteins; hemopexin; lipoproteins; sickle disease

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