

Comments on: “Impact of iron overload on interleukin-10 levels, biochemical parameters and oxidative stress in patients with sickle cell anemia”

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In the article, “Impact of iron overload on interleukin-10 levels, biochemical parameters and oxidative stress in patients with sickle cell anemia” by Barbosa et al.⁽¹⁾, the authors measured the levels of several biochemical blood components as well as oxidative stress status and interleukin 10 (IL-10) of a cross-sectional population of 30 sickle cell anemia patients, randomly selected of both genders and aged 38.5 ± 15.6 years. Participants were stratified into two groups of 15 patients each according to the presence of iron overload. Results showed significantly elevated levels of uric acid, triglycerides, very low-density lipoprotein (VLDL), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), urea, nitrite, creatinine and ferritin, and significant decreases in high-density lipoprotein (HDL), low-density lipoprotein (LDL), IL-10, catalase activity and malondialdehyde (MDA) levels in the group with iron overload. No significant differences were found for bilirubin and its fractions, hemoglobin, serum iron, and total cholesterol levels between the two groups. These biomarkers demonstrate the significant increase in oxidative stress and inflammation between sickle cell patients with and without iron overload. The major point of this study is to indicate that iron overload due to transfusion is an enhancing factor of oxidative stress and inflammation in sickle cell anemia.

Several studies have demonstrated significant increases in oxidative stress biomarkers and inflammation in sickle cell anemia patients compared to healthy controls⁽²⁻⁴⁾. However comparing the effect of iron overload between sickle cell patients provides a better means to characterize biomarker profiles in order to predict iron overload after chronic transfusions and thus prevent organ damage.

This case-control study of only 30 patients demonstrates a clear difference between sickle cell anemia patients with and without iron overload by evidence of a distinct pathophysiology response of the immune system and the oxidative stress to iron overload. This study also emphasizes the need to monitor transfusions very closely due to the toxicity of free iron, which will cause organ damage and even death. It is however not clearly discussed why and how the group of patients with iron overload had significantly less blood transfusions per year. This important detail is critical to take transfusion therapy with great caution even after few transfusions.

The analysis of the biochemical and oxidative stress parameters, as well as IL-10 levels, showed a clear increase of inflammation and tissue injury in the iron overload group. While each class of biomarker is traditionally thought to represent one of these processes, it is important to note that they are not distinct entities and have considerable interaction. Oxidative stress can initiate tissue injury and/or inflammation. Plasma MDA is a marker of tissue injury and oxidative stress. The free iron accumulation, due to transfusions, acts as a catalyst for oxidation with subsequent production of superoxide and hydroxyl radicals. The authors introduced the heme-oxidase-1 (HO-1) as one of the mechanisms induced by the reduction of bioavailability of nitric oxide. Heme-oxygenase is the rate-limiting enzyme in the degradation of heme groups to biliverdin, carbon monoxide (CO) and iron. Bilirubin is created by the activity of biliverdin reductase on biliverdin⁽⁵⁾, however, no significant differences in bilirubin and bilirubin derivate levels were observed between the two groups, perhaps suggesting a different mechanism involved to reduce superoxide and hydroxyl radicals.

Variability between sickle cell patients can be due to genetic polymorphisms and this kind of case-control study suggests that genetic research on this population may be of great interest to know the predisposition to iron overload. For example, it would be very interesting to know differences in the genotypes/haplotypes of the HO-1 gene (HMOX1) promoter polymorphism between the two groups as this was associated with susceptibility to several blood and immune diseases⁽⁶⁻⁸⁾.

Identification of specific biomarkers associated with iron overload will enable the development of precise diagnosis, targeted treatments and personalized follow ups in chronic transfusion therapy. The development and implementation of specific prevention therapies to control iron overload will require a more thorough understanding of the immunological mechanisms underlying the immune senescence across different populations and how this is modulated by environmental parameters such as exposure to infectious agents. The

discovery of biomarkers will help predict which individuals will be able to respond to therapies and design better ways to improve responses and ensure effective disease prevention.

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