Int J Cardiovasc Sci. 2022; 35(6), 780-783

EDITORIAL

Lipids and Sickle Cell Disease

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Editorial referring to the article: Association Between Lipid Profile and Clinical Manifestations in Sickle Cell Anemia: A Systematic Review

Sickle cell disease is a hereditary, autosomal recessive pathology caused by the replacement of adenine by thymin in position 6 of the beta globin gene, producing anomalous hemoglobin (hemoglobin S- HbS). It is characterized by a chronic inflammatory state with hemolytic anemia and vaso-occlusive phenomena and occurs when the HbS gene is in homozygosis (SS) or heterozygosis, in association with other variant hemoglobins (SD, SC, SE) or thalassemia[1] (Figure 1). Sickle cell disease is recognized by the World Health Organization (WHO) as a serious public health problem, and, despite advances in treatment, patients with sickle cell disease have a life expectancy of nearly 30 years lower than the general population.[2]

About 4% of the Brazilian population has a sickle cell trait, and between 60,000 and 100,000 Brazilians have the disease, which translates into an economic burden of more than US$ 400,000,000/year for the Brazilian society.[3] The number of patients affected by this pathology is increasing due to the evolution of treatment and improvement in early diagnosis, as a result of the institution of neonatal screening.[2] Early identification of the disease is important in reducing its morbidity and mortality, especially with the prophylaxis of infections, which are a significant cause of death in children. This improvement in survival leads to the development of chronic complications resulting from vasculopathy and to more frequent cases of chronic ischemia.[2]

Red blood cells with HbS polymerize when deoxygenated during their transit in capillary beds. These red blood cells have a higher endothelium adhesion and a lower survival due to hemolysis. Chronic hemolysis leads to reticulocytosis and endothelial dysfunction. It also triggers an inflammatory cascade by activating leukocytes, platelets, and endothelium,[4] with nitric oxide deficiency, oxidative stress, hypercoagulability,[2] and lipid profile alteration. Inflammation, hemolysis, and red blood cell sickling is responsible for acute and chronic organ injury. Recurrent episodes of ischemia and reperfusion cause vasculopathy and multiple organ damage.[5] Although the understanding of the pathophysiology of the disease has evolved, many questions still remain, primarily about the relationship between these diverse mechanisms and their contribution to the various types of complications.

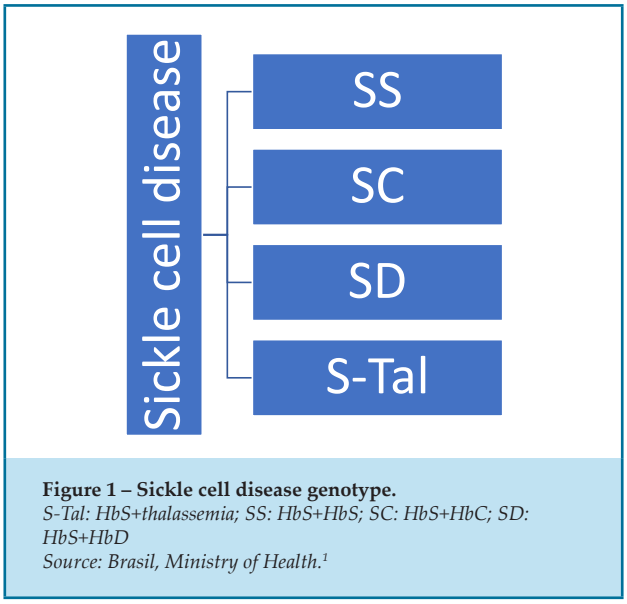

Figure 1 – Sickle cell disease genotype.
S-Tal: HbS+thalassemia; SS: HbS+HbS; SC: HbS+HbC; SD: HbS+HbD
Source: Brasil, Ministry of Health.[1]

Cardiovascular complications are common in sickle cell disease and an important cause of early mortality. They are characterized mainly by heart failure, pulmonary hypertension, and vasculopathy, including stroke.[5,6] In addition, kidney and liver diseases also contribute to higher mortality.

Keywords

Sickle cell disease; sickle cell anemia; dyslipidemias; hemoglobinopathies.

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DOI: https://doi.org/10.36660/ijcs.20220169

Heart disease occurs both by the effect of anemia and by the effect of polymerized HbS. Diastolic cardiac dysfunction is common, as are arrhythmias and sudden death. With the longer survival of these patients, cardiac complications become increasingly frequent.

In addition to acute thoracic syndrome, a classic complication of sickle cell disease characterized by dyspnea, chest pain, and pulmonary infiltrate, these patients are also prone to both arterial and venous pulmonary hypertension, as well as venous thromboembolism due to hypercoagulability.

Cerebral vasculopathy is an important cause of morbidity and mortality, which is due to several factors, such as inflammation, endothelial dysfunction, and hypoxemia.[5] Stroke, which can be hemorrhagic or thrombotic, is frequent and recurrent in this population, even with blood pressure (BP) within the normal range, especially when prophylaxis with chronic transfusion is not performed in children with altered medical cerebral artery flow velocity. In addition to physical sequelae, it can also cause cognitive and growth deficits in children.

The clinical picture of the patient may vary in severity due to the influence of several factors. The main determinant of severity is the genotype. Patients with an SS genotype have a more severe clinical picture, with more severe anemia and more frequent vaso-occlusion episodes. The same is true in people with an association of HbS and certain types of thalassemia, such as beta. Other genotypes, such as hemoglobin SC, have a lighter clinical picture, but with a higher frequency of ocular complications. The presence of alpha thalassemia and a high level of fetal hemoglobin (HbF) contribute to a lighter clinical course.[4] Other possible disease modifiers include: access to the health system, lifestyle, climate, environmental pollution, smoking, and social determinants of health.[2,5]

The article by Dantas et al.,[7] in the current issue of Int. J. Cardiovasc. Sci performs a meta-analysis of the lipid profile in patients with sickle cell disease in order to evaluate the association between the lipid profile and clinical manifestations of sickle cell disease. The publication evaluated 15 articles, 14 cross-sectional studies and one cohort study, all with a low risk of bias, except for two, with moderate risk. The most frequent findings were hypocholesterolemia and hypertriglyceridemia, which were correlated with clinical and laboratory findings of the disease (Table 1), including greater severity, suggesting a role of lipids in the mechanisms of inflammation and vascular damage involved in the multifactorial pathogenesis of sickle cell disease.

Alteration of lipid metabolism has been described in several inflammatory and vascular diseases, with a reduction in the high-density lipoprotein cholesterol (HDL-C) and an increase in the low-density lipoprotein cholesterol (LDL-C) risk factor for atherosclerotic disease. Some factors present in pathogenesis are shared between atherosclerosis and sickle cell disease, such as endothelial dysfunction, oxidative stress, and reduction in nitric oxide.[8] The lipid profile in sickle cell disease has been described in several studies.[9] The presence of hypocholesterolemia and hypertriglyceridemia is consistent, as demonstrated in Dantas et al.[7]

The correlation between blood lipid levels and clinical findings and other complementary test findings can help us understand the role lipids play in these patients. Hypocholesterolemia and hypertriglyceridemia were correlated with more severe anemia and the need for increased transfusion, as well as a higher risk of pulmonary and cardiac complications.

Whether these findings indicate a role of lipids in the pathogenesis of these complications, or whether they can be used as early markers and used in clinical practice to indicate the need for additional investigations or early therapies, is still an unanswered question. Further studies are needed to better understand this correlation. One question to be answered is if these lipid alterations are associated with a higher degree of anemia and whether transfusion needs would be more frequent in the SS genotype or in another characterized by a greater severity of the disease. It is important for further studies to correlate these findings with genotypes, as this may be a confounding factor, considering that they were observational studies.

In an era in which hematopoietic stem cell transplantation and gene therapy are being used for curative purposes and where patients show improvement in cardiac alterations after transplantation,[5] knowledge of the role of lipids in the pathogenesis of sickle cell disease complications is an important step in the search for a better quality of life and the prevention of complications in a debilitating and stigmatizing disease.

Table 1 – Main associations between lipid profile and sickle cell disease's clinical manifestations

LIPID ABNORMALITIES	CLINICAL MANIFESTATION
↓HDL-C	Cardiac abnormalities
	Pneumonia
	Priapism
	More severe anemia
	Vaso-occlusive syndrome
	High blood transfusion rates
↓TC	Pulmonary hypertension
	Priapism
	Vaso-occlusive syndrome
	More severe anemia
	Lower limb ulcers
↑TC	Cholelithiasis
	Pneumonia
↑TG	Cholelithiasis
	Electrocardiographic abnormalities
	Acute thoracic syndrome
	↑ or Vaso-occlusive syndrome
	More severe anemia
	↑ Pulmonary hypertension markers
	↑ BP (relative)
↑VLDL-C	Cholelithiasis
	↑ diastolic BP
	↓ systolic BP
↑LDL-C	↓ Lower limb ulcers
	↓ severe anemia
	Cholelithiasis
	Vaso-occlusive syndrome

HDL-C: high-density lipoprotein cholesterol; TC: total cholesterol; TG: triglycerides; VLDL-C: very low-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; BP: blood pressure.
Source: Dantas et al.[7]

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