Association Between Lipid Profile and Clinical Manifestations in Sickle Cell Anemia: A Systematic Review
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Abstract

Introduction: Sickle cell anemia (SCA) is a genetic disease associated with frequent episodes of acute illness. Changes in the lipid profile and a chronic inflammatory process make up the molecular aspects observed in this disease. Associations between these mechanisms and clinical manifestations could thus define severity profiles and therapeutic strategies.

Objectives: To verify whether there is an association between lipid profile and clinical manifestations in patients with SCA and if there is a correlation between lipid profile and laboratory markers in this disease.

Methodology: According to the PRISMA guidelines, a systematic review of the literature was conducted by searching the MEDLINE/PubMed, LILACS, SciELO, Scopus, and Cochrane databases. Articles were screened by reading the titles and abstracts, reaching those selected for full-text reading. The included studies were published between 2010 and 2020, were fully available in the databases, and addressed the proposed theme. The risk of individual bias was assessed by using the Joanna Briggs Institute checklist and the Newcastle-Ottawa scale.

Results: Out of the 144 identified articles, 15 were selected for analysis, resulting in a sample size of 2,230 individuals. HDL-C, LDL-C, total cholesterol, and triglycerides were the main variables analyzed in the lipid profiles. A correlation was observed between these variables and some of the most relevant clinical events in the disease, including vaso-occlusive seizures and acute thoracic syndrome.

Conclusion: Lipid metabolism disorders, especially hypocholesterolemia and hypertriglyceridermia, are linked to clinical events observed in SCA, suggesting they play a relevant role in the multifactorial pathogenesis of this disease.

Keywords: Anemia, Sickle Cell; Lipids; Signs and Symptoms.
Changes in the lipid profile of patients with SCA have been well documented by several studies. Low levels of total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) define hypocholesterolemia, while increased triglycerides reveal hypertriglyceridemia. Several hypotheses may explain these findings, but lack scientific evidence. Studies on dyslipidemia in patients with SCA have been restricted to cholesterol metabolism, and a knowledge gap remains on how this lipid alteration is associated with comorbidities of the disease. The aim of this study was thus to verify whether there is an association between lipid profile and clinical manifestations of SCA.

Methods

Study Design

This is a systematic review based on recommendations by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA); its protocol was registered in the International Prospective Registry of Systematic Reviews (PROSPERO) under registration number CRD42020214778.

Search Strategy

The search and selection of studies were performed in the MEDLINE/PubMed, LILACS, SciELO, Scopus, and Cochrane databases. Each database was explored using an individualized strategy consisting of descriptors among the Medical Subject Headings (MeSH) and Health Sciences Descriptors (DeCS) corresponding to "sickle cell anemia," "sickle cell disease," "lipids," "lipid," "clinical manifestations," "signs," "symptoms," and "comorbidity." Additionally, a manual search was performed in the reference lists of the selected articles to uncover studies missed in the database searches. The databases were last accessed on October 25, 2020.

Eligibility Criteria

Original studies published and available in full in the scientific databases or in printed versions, such as observational studies (cross-sectional, cohort, and case-control), experimental studies (clinical trials), and review studies, published between 2010 and 2020, in English and/or Portuguese, addressing the association between lipid profile and clinical manifestations in patients with SCA.

Results

A total of 144 citations were identified in the electronic databases. After removal of duplicate articles and selection by reading the titles, abstracts, and full texts, 15 articles were included in our qualitative synthesis. The flowchart presenting the study selection process is presented in Figure 1.

Characteristics of the included studies

Among the 15 selected articles, 14 were cross-sectional studies and one was a cohort study. The years of publication ranged from 2010 to 2020. The sample size ranged from 81 to 367 participants, with a total of 2,230 individuals included in all 15 studies; 1,849 (82.9%) participants had sickle cell disease and 381 (17.1%) were healthy individuals. HDL-C was analyzed in all studies. TC, triglycerides (TG), and LDL-C were analyzed by 14, 13, and 12 studies, respectively. Very low-density lipoprotein (VLDL) and TG/HDL appeared in five of the articles and non-HDL C was reported in two studies, while pro-HDL and TC/HDL were mentioned by one study each. Table 1 presents the characteristics of the studies, the analyzed variables, and their main results.
Figure 1 – Study selection flowchart.

Studies identified by searching the databases (n = 144)

- PubMed n = 108
- LILACS n = 6
- Scielo n = 3
- Scopus n = 21
- Cochrane n = 6

Studies left after removing duplicates (n = 126)

Studies excluded by reading the title (n = 84)

Studies selected after reading the title (n = 42)

Studies excluded by reading the abstract (n = 27)

Studies selected for full-text reading (n = 15)

Studies added from reference lists (n = 5)

Excluded studies:
- Not fully available (n = 1)
- Did not address the topic of the review (n = 4)

Studies selected for reviewing (n = 15)
Main outcome

A reduction in HDL-C levels was associated with history of cardiac abnormalities, pneumonia, priapism, and greater need for blood transfusion, in addition to hematological parameters of more severe anemia (2, 8, and 9). Two studies showed that high HDL-C levels were related to a higher frequency of vaso-occlusive seizures (VOS) (7 and 14). Decreased TC levels were found in patients with suspected pulmonary hypertension (PH), history of priapism and ulcers in the lower limbs, and individuals with VOS (2 and 3); they were also correlated with more severe anemia (1). Elevated TC levels were associated with cholelithiasis (8) and a history of pneumonia (7). Increased TG levels showed a positive correlation with cholelithiasis (8), in addition to electrocardiographic abnormalities (4), history of acute thoracic syndrome (ATS), VOS, more severe anemia (6), elevated markers of PH (9), and relative hypertension in patients with SCA (BP ≥ 120/70 mmHg and < 140/90 mmHg) (11). Conversely, one study showed a negative correlation between VOS and TG, as well as between VOS and LDL-C (3). LDL-C also showed a negative correlation with lower limb ulcers (6) and anemia severity (7), and a positive correlation with cholelithiasis (8) and pneumonia (6). Elevated VLDL levels were also associated with cholelithiasis (8), reduced systolic blood pressure, and increased diastolic blood pressure (12). Pro-HDL showed a positive correlation with suspected PH and a negative correlation with priapism (2). High TG/HDL ratios were associated with a higher number of ATS and VOS episodes and had a positive correlation with lactate dehydrogenase (LDH), leukocyte count, and flow velocity in the right and left cerebral arteries; a negative correlation with Hb levels was also observed for this parameter (6). In one of the studies, ATS, VOS, and osteonecrosis were not affected by TC, HDL-C, and LDL-C levels (10); in another study, no correlation was found between these parameters and markers of PH (9). One study explored hearing loss in patients with SCA, not verifying any associations between lipid profile and such outcome (5).

Quality of the included studies

In the evaluation of cross-sectional studies, among the 14 articles analyzed in this review, 12 presented a low risk of bias (70%-100% of “Yes” answers in the JBI checklist), while 2 studies were classified as having a moderate risk of bias (50%-69% of “Yes” answers) – Appendix I. The main limitations of cross-sectional studies were the identification and control of potential confounding factors. Some of the studies also did not specify the criterion used to confirm the HbSS genotype (eg, hemoglobin electrophoresis or liquid chromatography). The only cohort study included in this review was evaluated with the Newcastle-Ottawa Scale for Cohort Studies – Appendix II, which showed a high level of evidence (8 in a 9-point scale).

Discussion

The alterations in lipid metabolism found in patients with SCA are marked by hypocholesterolemia and hypertriglyceridemia. The main mechanisms proposed to justify hypocholesterolemia are: (1) increased cholesterol consumption for the synthesis of new red blood cells due to lower survival or increased hemolysis; and (2) dilution of serum cholesterol by decreased erythrocytic mass and increased plasma volume. In addition, reduced liver function can lead to lower cholesterol production and increased TG. Chronic anemia induces catabolism, which generates greater release of free fatty acids; their increased supply to the liver leads to higher TG production.

The analyzed studies showed an association between lipid profile and clinical events observed in SCA. HDL-C, TC, TG, and LDL-C were among the most frequently explored variables.

Five studies showed an association between reduced HDL-C levels and clinical complications or markers of more severe anemia. Low HDL-C was found in patients with history of priapism by Ataga et al. (2015); history of cardiac abnormalities, pneumonia, and greater need for blood transfusion were found by Seixas MO et al. (2010). Therefore, HDL was not only a potential biomarker of clinical severity, but also linked to laboratory worsening of the disease. Regarding TC, Zorca et al. (2010) reported an inverse correlation between TC levels, HDL-C, and LDL-C and anemia severity. This evidence was corroborated by Valente-Frossard et al. (2020) and Emokpae, Kuliya-Gwarzo (2014), who also observed worsening of inflammation, with increased leukocytes, monocytes, and platelets. Emokpae reinforced the correlation between reduced HDL-C and a greater need for blood transfusions, in addition to a higher frequency of VOS. In this sense, Aleluia et al. (2017) bring evidence of a direct association between HDL-C and fetal hemoglobin (HbF), whose role is important to prevent...
<table>
<thead>
<tr>
<th>Author and year of publication</th>
<th>Country</th>
<th>Title</th>
<th>Population</th>
<th>Lipid profile analyzed</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aleluia MM et al. (2017)</td>
<td>Brazil</td>
<td>Association of classical markers and establishment of the dyslipidemic subphenotype of sickle cell anemia</td>
<td>99 HbSS patients in steady state</td>
<td>TC, HDL-C, LDL-C, VLDL-C, TG</td>
<td>HDL-C levels greater than 40.0 mg/dL were associated with an improvement in hematological parameters (red blood cell count, Hb, and Ht), in addition to an increase in HbF.</td>
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<tr>
<td>Ataga KI et al. (2015)</td>
<td>USA</td>
<td>Association of pro-inflammatory high-density lipoprotein cholesterol with clinical and laboratory variables in sickle cell disease</td>
<td>117 patients with sickle cell disease: (91 HbSS; 13 HbSC; 5 HbSβ0-thalassemia and 8 HbSβ+-thalassemia) in addition to 11 healthy patients (control)</td>
<td>TC, HDL-C, Pro-HDL</td>
<td>Pro-HDL was increased in patients with suspected pulmonary hypertension and decreased in patients with history of priapism. TC was reduced in patients with suspected pulmonary hypertension. There was a trend towards lower TC levels in patients with history of priapism and ulcers in the lower limbs. HDL was also decreased in patients with history of priapism.</td>
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<tr>
<td>Akinlade KS et al. (2014)</td>
<td>Nigeria</td>
<td>Defective lipid metabolism in sickle cell anaemia subjects in vaso-occlusive crisis</td>
<td>58 HbSS adults (30 in steady state and 28 in vaso-occlusive crisis) in addition to 24 healthy adults (control)</td>
<td>TC, HDL-C, LDL-C, TG, TG/HDL</td>
<td>TC, LDL, TG, and TG/HDL were significantly reduced while HDL was increased in patients in vaso-occlusive crisis when compared to patients in a stable disease state.</td>
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<td>Adegoke SA et al. (2016)</td>
<td>Nigeria</td>
<td>Electrocardiographic abnormalities and dyslipidaemic syndrome in children with sickle cell anaemia</td>
<td>62 HbSS children and 40 healthy people of the same age group</td>
<td>TC, HDL-C, LDL-C, TG</td>
<td>TG levels showed a positive correlation with the PR interval. Mean TG levels were significantly elevated in patients with SCA and ECG abnormalities compared to those with a normal ECG.</td>
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<tr>
<td>Rissatto-Lago MR et al. (2018)</td>
<td>Brazil</td>
<td>Hidden hearing loss in children and adolescents with sickle cell anemia</td>
<td>37 HbSS patients in steady state and 44 healthy controls (all 6-18 years of age)</td>
<td>TC, HDL-C, LDL-C, TG, TG/HDL</td>
<td>No association was observed between lipid profile and increased acoustic reflex thresholds.</td>
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<tr>
<td></td>
<td>Authors</td>
<td>Country</td>
<td>Study Design</td>
<td>Participants</td>
<td>Results</td>
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<td>6</td>
<td>Teixeira RS et al. (2019)</td>
<td>Brazil</td>
<td>Higher TG/HDL-cholesterol ratios hallmark disease severity in children and adolescents with sickle cell anemia</td>
<td>55 HbSS patients in steady state and 41 healthy controls (all 6-18 years of age)</td>
<td>Elevated TG/HDL in patients with SCA was associated with more episodes of acute chest syndrome and vaso-occlusive crises. TG/HDL also had a positive correlation with LDH, WBC count, and flow velocity in the right and left cerebral arteries, in addition to a negative correlation with Hb levels.</td>
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<tr>
<td>7</td>
<td>Guarda CC et al. (2020)</td>
<td>Brazil</td>
<td>Investigation of Lipid Profile and Clinical Manifestations in SCA Children</td>
<td>126 HbSS patients in steady state</td>
<td>Patients with history of pneumonia had increased levels of TC and LDL-C. Previous history of lower limb ulcers was associated with reduced LDL-C levels. Individuals with history of pain crises presented elevated HDL-C levels.</td>
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<td>8</td>
<td>Seixas MO et al. (2010)</td>
<td>Brazil</td>
<td>Levels of high-density lipoprotein cholesterol (HDL-C) among children with steady-state sickle cell disease</td>
<td>152 HbSS children in steady state and 132 healthy children</td>
<td>Decreased HDL-C levels were associated with a history of cardiac abnormalities, pneumonia, and need for blood transfusion. Elevated levels of TC, LDL-C, VLDL-C, and TG were associated with the occurrence of cholelithiasis.</td>
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<td>9</td>
<td>Zorca S et al. (2010)</td>
<td>USA</td>
<td>Lipid levels in sickle-cell disease associated with haemolytic severity, vascular dysfunction and pulmonary hypertension</td>
<td>328 adults with SCA in a stable state (250 SS or Sβ0 and 78 SC or Sβ+) and 39 healthy controls</td>
<td>TC, HDL-C, and LDL-C were inversely correlated with anemia severity, but not with markers of pulmonary hypertension (NT-proBNP and TRV). Serum TG levels were positively correlated with markers of pulmonary hypertension.</td>
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<td>10</td>
<td>Lalanne-Mistrih ML et al. (2018)</td>
<td>Guadalupe (France)</td>
<td>Lipid profiles in French West Indies sickle cell disease cohorts, and their general population</td>
<td>159 adults with SCA in steady state (97 HbSS and 62 HbSC)</td>
<td>Patients with elevated TG showed history of acute chest syndrome more frequently. Acute chest syndrome, vaso-occlusive crises, and osteonecrosis were not affected by TC, HDL-C, and LDL-C levels.</td>
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<td>11</td>
<td>Lamarre Y et al. (2013)</td>
<td>Guadalupe (France)</td>
<td>Male Gender, Increased Blood Viscosity, Body Mass Index and Triglyceride Levels Are Independently Associated with Systemic Relative Hypertension in Sickle Cell Anaemia</td>
<td>97 HbSS adults in steady state</td>
<td>Elevated TG levels could increase the risk of developing relative hypertension (BP ≥ 120/70 mmHg and &lt; 140/90 mmHg) in SCA. Patients with borderline/elevated TG levels had history of acute chest syndrome and vaso-occlusive crises more frequently.</td>
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<tr>
<td>Study</td>
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<td>Year</td>
<td>Country</td>
<td>Participants</td>
<td>Measurements</td>
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<td>12</td>
<td>Ephraim RKD et al. (2016)</td>
<td>Ghana</td>
<td>Normal Non-HDL Cholesterol, Low Total Cholesterol, and HDL Cholesterol Levels in Sickle Cell Disease Patients in the Steady State: A Case-Control Study of Tema Metropolis</td>
<td>50 patients with SCA (12 HbSS and 38 HbSC) in a stable state and 50 healthy controls</td>
<td>TC HDL-C LDL-C Non-HDL TG TG/HDL</td>
</tr>
<tr>
<td>13</td>
<td>Valente-Frossard TNS et al. (2020)</td>
<td>Brazil</td>
<td>Polymorphisms in genes that affect the variation of lipid levels in a Brazilian pediatric population with sickle cell disease: rs662799 APOA5 and rs964184 ZPR1</td>
<td>161 children and adolescents with SCA (92 HbSS and 69 HbSC) in a stable state</td>
<td>TC HDL-C Non-HDL TG CT/HDL TG/HDL</td>
</tr>
<tr>
<td>14</td>
<td>Darbari DS et al. (2013)</td>
<td>USA</td>
<td>Severe painful vaso-occlusive crises and mortality in a contemporary adult sickle cell anemia cohort study</td>
<td>264 HbSS adults</td>
<td>HDL-C</td>
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<tr>
<td>15</td>
<td>Emokpae A, Kuliya-Gwarzo A (2014)</td>
<td>Nigeria</td>
<td>The influence of decreased levels of high density lipoprotein cholesterol on hematological indices in sickle cell disease patients</td>
<td>84 patients with SCA in a stable state (all from 15 years old)</td>
<td>TC HDL-C LDL-C VLDL-C TG</td>
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Note: All studies included in the review adopted a statistical significance level of 5%. 
the polymerization of HbS and increase the survival of red blood cells, consequently reducing the occurrence of VOS and hemolysis.\textsuperscript{18,19} Lower HbF levels thus may represent one of the pathophysiological mechanisms that lead to a greater severity of SCA in patients with low HDL-C.

Conversely, two retrospective studies, Guarda et al. (2020)\textsuperscript{20} and Darbari et al. (2013),\textsuperscript{21} found an association between higher HDL-C levels and more frequent VOS. Lalanne-Mistrih et al. (2018),\textsuperscript{22} also through a retrospective analysis, did not detect a correlation between clinical history of VOS and this lipid component. However, due to their retrospective nature, these studies present a higher risk of bias. It is noteworthy that VOS result from a pathological process that involves oxidative stress, increased expression of endothelial adhesion molecules, inflammatory cytokines, and nitric oxide depletion. These factors, associated with a lipid profile disorder, create a positive feedback loop for the chain of inflammation that leads to vaso-occlusive phenomena.\textsuperscript{23}

In patients with SCA, PH has already been attributed to endothelial injury resulting from chronic hemolysis, smooth muscle dystonia, and nitric oxide depletion vasculopathy.\textsuperscript{24} However, Ataga et al. (2015)\textsuperscript{25} observed reduced TC levels in patients with suspected PH when compared to those without this suspicion, as well as a negative correlation between TC and soluble vascular cell adhesion molecule-1 (sVCAM-1), suggesting that hypocholesterolemia contributes to the endothelial activation involved in PH. In disagreement, Zorca et al. (2010)\textsuperscript{44} did not identify an association between TC and markers of PH, such as N-terminal B-type natriuretic peptide (NT-proBNP) and tricuspid regurgitation velocity (TRV), or a correlation with markers of endothelial dysfunction, including sVCAM-1.

Guarda et al. (2020)\textsuperscript{20} reported high TC levels in patients with history of pneumonia. It is known that pulmonary complications in SCA are associated with vascular damage and vasoconstriction, proposing a significant involvement of cholesterol in these mechanisms. The occurrence of pneumonia in SCA is often associated with ATS, and these conditions often overlap. However, in a study conducted by Lalanne-Mistrih et al. (2018),\textsuperscript{22} ATS was not affected by TC levels. These data suggest that the role of cholesterol in pulmonary events still needs to be defined.

Cholelithiasis was associated with high levels of TC, LDL-C, VLDL-C, and TG, according to Seixas et al. (2010).\textsuperscript{12} It is understood that these lipids have an indirect effect on the formation of gallstones, considering that stones seen in patients with SCA and other hemolytic anemias are pigmented, composed mainly of calcium bilirubinate, and caused by indirect hyperbilirubinemia secondary to chronic hemolysis.

Lower levels of LDL-C were found in patients with history of lower limb ulcers, while above-average levels were observed in patients with history of pneumonia.\textsuperscript{20} Several mechanisms have been suggested to explain the pathophysiology of ulcers in SCA, including physical obstruction caused by sickle red blood cells, poor venous recirculation, reduced nitric oxide bioavailability, and susceptibility to infections. Lipid alterations are thus understood as part of a multifactorial pathogenic process and not as a direct causative agent of this clinical complication.

The higher prevalence of electrocardiographic abnormalities in patients with SCA is well demonstrated when comparing them to healthy individuals. Adegoke et al. (2016)\textsuperscript{25} demonstrated that children with SCA were six times more likely to present left ventricular hypertrophy and had a higher prevalence of first-degree atrioventricular block and T-wave alterations compatible with lateral ischemia. These changes result from an increased cardiac output secondary to chronic anemia, leading to volume overload and eccentric hypertrophy.\textsuperscript{44} This study also demonstrated higher TG levels in children with SCA and electrocardiographic abnormalities, suggesting that dyslipidemia is a potential biomarker for electrocardiographic changes in these patients. In this perspective, TG were significantly correlated with markers of hemolysis, endothelial activation, and inflammation, being directly linked to vascular dysfunction; the repercussions of this dysfunction occur in both the macro and microcirculation, harming different vascular sites, including the heart.

Zorca et al. (2010)\textsuperscript{44} showed a positive correlation of TG with NT-proBNP and TRV, which are markers of PH. It is thus possible that the vasculopathy induced by hypertriglyceridemia has as its main target, within SCA, the pulmonary vasculature, contrary to what is observed in the general population in which the most affected tissues are the coronary and cerebral arteries. Still considering the effects of this vasculopathy, Lalanne-Mistrih et al. (2018)\textsuperscript{22} reported a higher frequency of ATS in patients with high TG levels; this evidence was ratified by Lamarre et al. (2013),\textsuperscript{26} who also observed an association with a higher frequency of VOS. These
outcomes attest to the negative impact of TG on vascular function. In addition, increased systolic blood pressure, even if lower than 140 mmHg, is associated with an increased risk of stroke and mortality in patients with SCA. To this condition, Lamarre attributed the term "relative hypertension," demonstrating that increased TG levels were a relevant risk factor for its development.

The TG/HDL ratio is also an important lipid parameter. This marker shows a strong correlation with cardiovascular risk, being a good predictor of acute myocardial infarction and associated with insulin resistance. A study by Teixeira et al. (2019) found the role of TG/HDL as a marker of vascular damage in patients with SCA, finding correlations with markers of hemolysis (LDH and hemoglobin) and with the increase in blood flow velocity in the middle cerebral arteries on transcranial Doppler; this last parameter is an important predictor of stroke in these patients. Vascular damage was also evident by the association of an increased TG/HDL ratio with a higher number of episodes of ATS and VOS: children with TG/HDL values above 2.93 were 3.77 times more likely to present at least one of these clinical events.

The possible limitations of this review are linked to disparities between the populations of the included studies, such as the heterogeneity in sample sizes, age groups, and SCA phenotypes. On the other hand, the low risk of bias in most of the included studies and the rigor in complying with the PRISMA protocol ensure the methodological quality of this study. The registration in PROSPERO qualifies the transparency and scientific integrity of this review.

**Conclusion**

Lipid metabolism disorders, especially hypocholesterolemia and hypertriglyceridemia, are linked to the occurrence of clinical events observed in patients with SCA, suggesting a relevant role in the multifactorial pathogenesis of this disease.

This study demonstrated the association between lipid profile and clinical events in SCA, as well as a correlation between lipids and laboratory markers of the disease. The derangement of the lipid metabolism, marked by hypocholesterolemia and hypertriglyceridemia, was found to be linked to clinical manifestations that constitute a more severe course of the disease, suggesting an important involvement of these lipids in the processes of inflammation and vascular damage that comprise the multifactorial pathogenesis of SCA.

**Author contributions**

Conception and design of the research and critical revision of the manuscript for intellectual content: Dantas MT, Ladeia AMT; acquisition of data and writing of the manuscript: Dantas MT; analysis and interpretation of the data: Dantas MT, Lopes AC.

**Potential Conflict of Interest**

No potential conflict of interest relevant to this article was reported.

**Sources of Funding**

There were no external funding sources for this study.

**Study Association**

This study is not associated with any thesis or dissertation work.

**Ethics approval and consent to participate**

This article does not contain any studies with human participants or animals performed by any of the authors.

**References**


*Supplemental Materials*

For additional information, please click here.