Received: 10 May 2023 | Revised: 15 September 2023 | Accepted: 19 September 2023

DOI: 10.1002/hsr2.1609

NARRATIVE REVIEW

Health Science Reports Open Access WILEY

Homozygote drepanocytosis: Ferric status and inflammation in world and Africa: Review article and meta analysis

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Abstract

Background and Aims: Major sickle cell syndromes are subjected to a high frequency of hemolysis, infections, oxidative stress, and vasoocclusive crises which promote inflammation and iron balance disorders. We aimed to systematically review and analyze the studies in this patients addressing in general, and Africa in particular.

Methods: The systematic review of published articles in the Pubmed and Google Scholar databases was carried out according to the recommendations of the PRISMA model. The case-control articles have been included. The data extracted from the articles were analyzed using statistical software R. The standardized mean difference (SMD) was used to assess the extent of the disease on the different variables studied.

Results: At the end, 128 articles were obtained; but only 33 were elligible for meta-analysis. A SMD of −1.79 was obtained for hemoglobin between the sickle cell patients and the controls due to the deviation from the overall mean hemoglobin in the cases (8 ± 2 g/dL) and in controls (13 ± 3 g/dL). Sickle cell disease showed a significant extent on ferritin [SMD = 2.61; (95% confidence interval, CI: 2.39–2.83); ($p < 0.01$)] compared to non-sickle cell patients thus describing a higher risk for sickle cell sufferer to have ferritin disorders. The included studies also described the influence of sickle cell anemia on serum iron [SMD = 1.52; (95% CI: 1.32–1.76); ($p < 0.01$)] compared to normal subjects. The high risk of inflammation has been described as higher in sickle cell patients [SMD = 0.38; (95% CI: 0.25–0.50)], reflecting the moderate extent of sickle cell disease on inflammation.

Conclusion: Patients with major sickle cell syndrome in inflammation have a higher risk of iron profile disorders compared to the normal population. Further studies are needed to explore mechanisms for preventing the deleterious effects of iron from this hemolysis, for example haptoglobin genotyping.

KEYWORDS

ferritin, hemoglobin, hemolysis, inflammation, serum iron, sickle cell anemia

1 | INTRODUCTION

Major sickle cell syndromes are genetic diseases of autosomal recessive inheritance. They include three main genetic forms: homozygotic S/S, heterozygotic composites S/C and S/β° or S/β+ thalassemias. Sickle cell disease is an inherited, co-dominant, autosomal recessive disease characterized by the presence of abnormal hemoglobin (Hb S) in the blood. It is associated with multiple acute and chronic complications such as vaso-occlusive crises, acute anemia, splenic sequestration, erythroblastopenia.[1] It is among the most common monogenic diseases worldwide.[2] It is estimated that there are 312,000 new sickle cell patients worldwide, including 236,000 in Sub-Saharan Africa.[3] Major sickle cell syndromes are very prevalent in Africa and Asia. These genetic disorders are manifested by frequent vasooclusive crises, causing ischemia and/or episodic necrosis. Seizures in extreme cases can cause severe damage to organs affecting the brain, skeleton, pulmonary vascular system, spleen and liver, leading to increased morbidity and mortality in patients.[4] These described manifestations are important factors of inflammation in sickle cell patients.[5] Several authors report a significant elevation of proinflammatory cytokines in sickle cell patients including Bandeira et al.[6] and Zahrane et al.[7] In a patient with major sickle cell syndrome, during the inflammatory reaction, there is an overproduction of interleukin 6 which induces the synthesis of hepcidin, the central molecule of iron metabolism.[5] Previous works showed that hepcidin in serum has a strong positive correlation with serum ferritin levels in patients with anemia associated with inflammatory conditions.[8] The elevation of inflammatory markers in sickle cell patients as described by the authors is associated with dysregulation of the iron profile thus contributing to maintain the inflammatory vicious circle by the oxidizing properties of the iron produced. Furthermore, haptoglobin is a molecule with anti-inflammatory and antioxidant properties which could reduce the consequences of iron from inflammation. Haptoglobin is a serum glycoprotein of hepatocytic origin, migrating electrophoretically in the area of α two-globulins. It is well known that haptoglobin possess three phenotypes/proteins, which differ in number, type of chain and their molecular weight: phenotype Hp 1-2, phenotype Hp 1-1, and phenotype Hp 2-2.[9] These proteins are probably not equivalent; indeed, previous studies show that patients with the Hp 2-2 form would have more vascular complications.[10–12] Moreover, this genotype would have an oxidative action while the genotype Hp 1-1 has an antioxidant action.[13] According to Langlois et al.[14] the phenotype 2-2 is associated in adults with a significant elevation of serum iron, an increase in the transferrin saturation coefficient, an increase in ferritin followed however by a decrease in the concentration of soluble transferrin and/or transferrin receptors; Several other authors show the influence and impact of haptoglobin genotypes on the iron profile.[15,16]

The objective of this review article is to describe the iron balance disorders in sickle cell patients in inflammation in world in general, and Africa in particular; and provides insights into the anti-inflammatory and antioxidant properties of genotypes of haptoglobin.

2 | METHODS

The systematic review of published articles was carried out according to the recommendations of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyzes) model[17] and the Cochrane Handbook for Systematic Reviews of Interventions[18] focusing on the main issue which is the iron profile in sickle cell patients in an inflamed situation.

2.1 | Study search and selection strategy

The following databases were searched: PubMed, Google scholar. The MeSH terms and the keywords sickle cell anemia, inflammation, iron profile, were combined. The research for the studies was carried out over a period of 20 years; the research papers obtained were included. All included articles were written in English. Additionally, articles whose full text was not available were excluded.

2.2 | Selection of studies and data extraction

We included cross-sectional, and case-control studies. The included case-control articles consisted of both SS sickle cell patients in the stationary and intercritical phase (cases) and normal AA subjects (control). The protocol for the exhaustive search of published articles was set up on the basis of the main and valid keywords by two evaluators. Subsequently, an assessment of the articles to be included was made. The full texts of all citations that could meet the inclusion criteria were then retrieved and evaluated for final inclusion by both evaluators. All disagreements have been resolved for optimal selection.

Data extraction was done using an Excel spreadsheet 2016 and a second reading was done to examine data collected for accuracy and uniformity. The following data were extracted from the selected publications: Information surrounding the study (Title of the study, names of authors, country and year of publication), setting, sample characteristics (population size, age, sex), the methods used (study design, Statistical tools and tests used), study design (cross-sectional, or case-control) and the main results obtained.

2.3 | Ethical statement

Not applicable for this study.

2.4 | Data synthesis and analysis

A narrative description was first made to synthesize the information collected from all the included studies. Statistical analyses of the data were carried out using statistical software R version 3.5.0. The default fixed confidence interval (CI) for parameter analysis was 95%.

The standardized mean difference (SMD) was used to assess the mean absolute difference in score between the intervention group and the control group. SMD can be interpreted as the magnitude of the effect of the intervention compared to a control group. It was interpreted as follows: by consensus, the size of the effect was held to be small (0.2 to <0.3), moderate (0.3 to <0.8) or large (>0.8).[19] Heterogeneity between included studies was investigated. An I^2 value <0.25 (25%) indicates low heterogeneity, values between 0.25 (25%) and 0.5 (50%) moderate heterogeneity and a value >0.5 (50%) a significant heterogeneity.[19]

3 | RESULTS

3.1 | Review process

Initially, 128 studies were extracted from the different databases (PubMed 78 and Google scholar 50). After removing the duplicates, 98 articles were selected on the basis of their title and abstract; of these, 73 were selected for an in-depth full-text review. Articles whose full text was not available were excluded. Then of these studies, 33 were finally analyzed and included for meta-analysis (Figure 1).

3.2 | Included studies: General characteristics

The period of publication of the included studies was from 2004 to 2021. All of the included descriptive studies were conducted in sickle cell patients, some being homozygous and others being heterozygous; for the case-control studies, the study population was sickle cell and non-sickle cell patients. The population of the included studies consisted of people of all ages, and both sexes. Of the 33 included studies, 14 were from Africa,[7,20–30] 4 from Europe,[8,31–33] 8 from South America,[6,11,34–39] 4 from America,[40–43] 3 in Asia.[1,44–46] The included studies evaluated hemoglobin, ferritin, serum iron, C-reactive protein (CRP) and transferrin chiefly. Among these studies, those that have most attracted our interest are the case-control studies because they best describe the disorders of the iron profile in sickle cell patients in inflammation.

3.3 | Hemoglobin, sickle cell anemia versus the control

Eleven of the included case-control studies described hemoglobin in the study population for a study population size of 854 for cases and 562 for controls. The fixed model effect SMD obtained for all 11

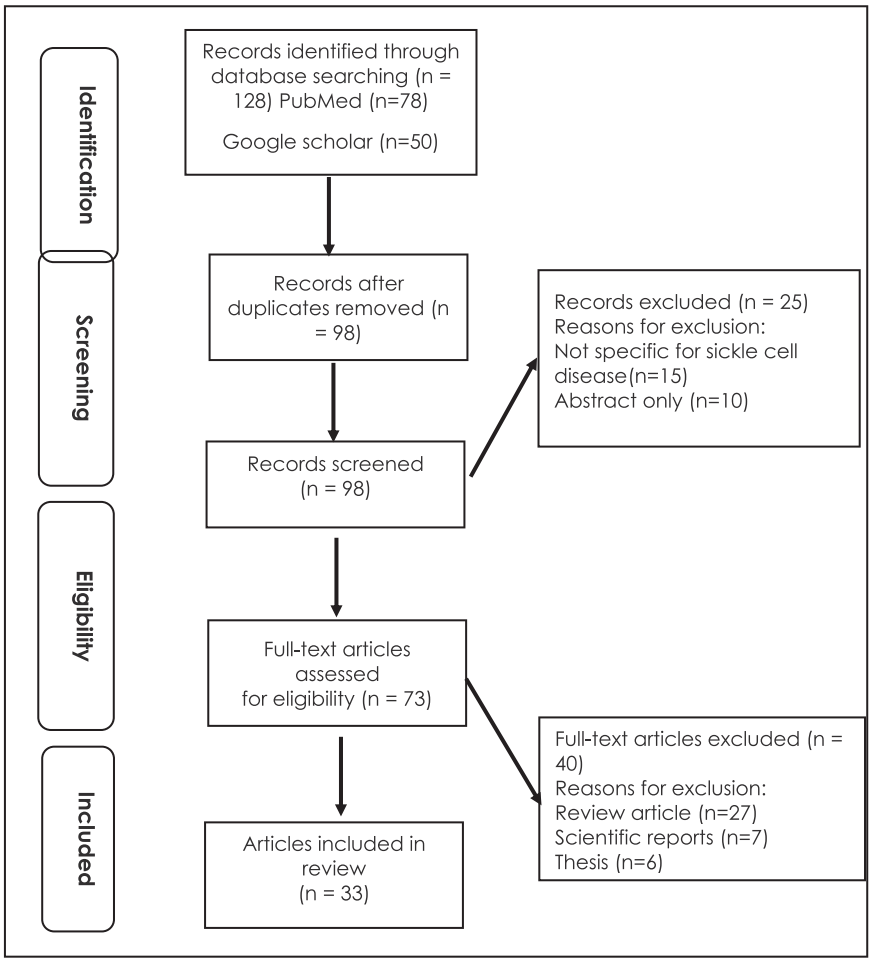

FIGURE 1 Flow diagram of the literature search.

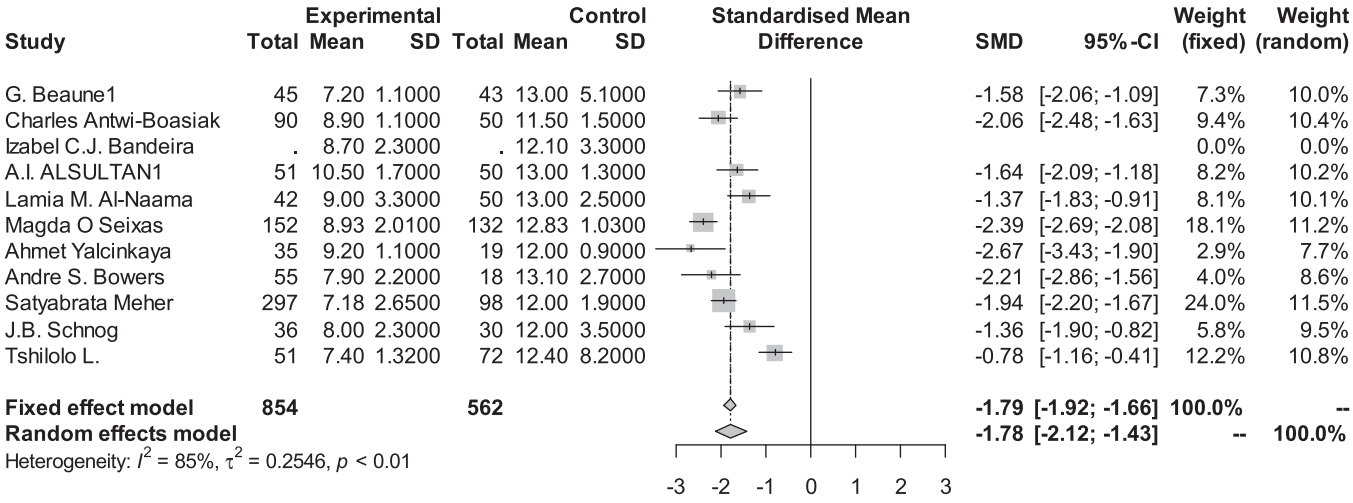

FIGURE 2 Hemoglobin from included studies.

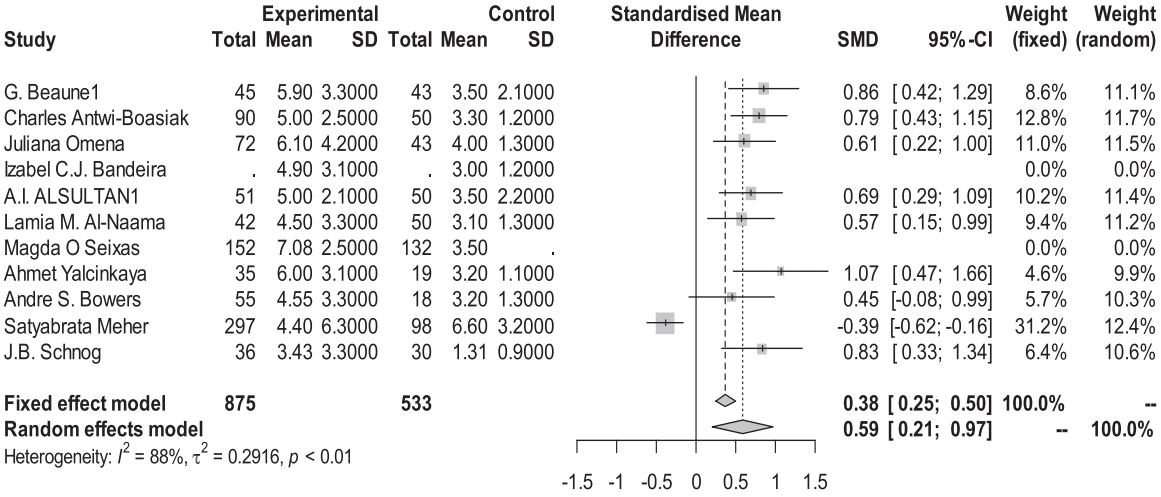

FIGURE 3 C-reactive protein from included studies.

studies was −1.79 due to the mean difference in hemoglobin between the sickle cell patients and the controls. In fact, there is a significant difference between the general mean hemoglobin in the cases (8 ± 2 g/dL) and in the controls (13 ± 3 g/dL). Thus, it shows the weak influence of sickle cell anemia and hemoglobin compared to the control population with [95% CI: (−1.92 to −1.86); (p < 0.01)]. The study with the largest SMD is that of Tshilolo et al.[47] with −0.78 [95% CI: −1.16; −0.41] (Figure 2).

3.4 | CRP, sickle cell disease versus control

Eleven of the included case-control studies described CRP in the study population for a total study population size of 875 for cases and 533 for controls. The difference in standardized mean obtained with a fixed model effect in these studies is 0.38, thus reflecting the moderate extent of sickle cell disease on inflammation compared to the control population with (95% CI: 0.25–0.50). The study that showed greater SMD is that of Yalcinkaya et al.[31] with 1.07 [CI: 0.47; 1.66); the one with the lowest SMD is that of Meher et al.[1] with −0.39 (CI: −0.33; −0.16) (Figure 3).

3.5 | Ferritin, sickle cell anemia against the control

Five of the included case-control studies described ferritin in the study population for a study population size of 386 for cases and 354 for controls. The SMD obtained with a fixed model effect for all the 05 studies is 2.61 thus reflecting the significant extent of sickle cell disease on ferritin compared to the control population with [95% CI: 2.39–2.83; (p < 0.01)]. The study with the largest SMD is that of Alsultan et al.[45] with a SMD of 15.17 [95% CI: 13.00; 17.34]; the one with the lowest SMD is that of Tshilolo et al.[47] with 1.31 [95% CI: 0.92–1.71] (Figure 4).

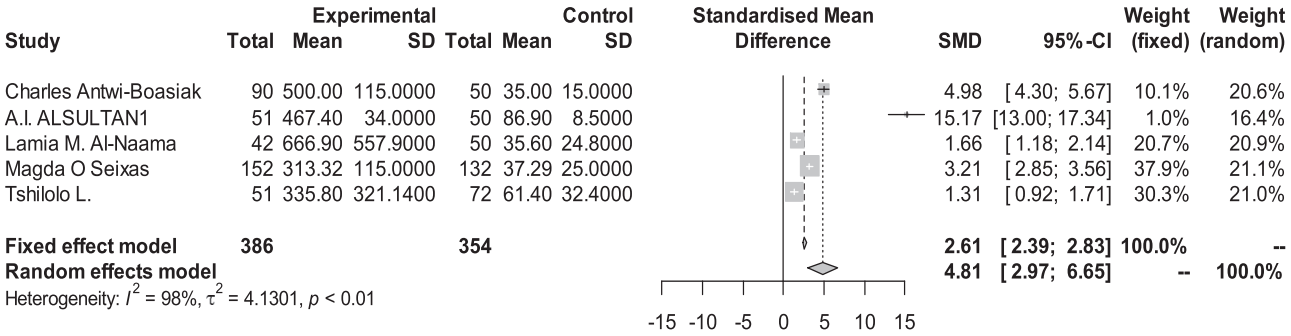

FIGURE 4 Ferritin from included studies.

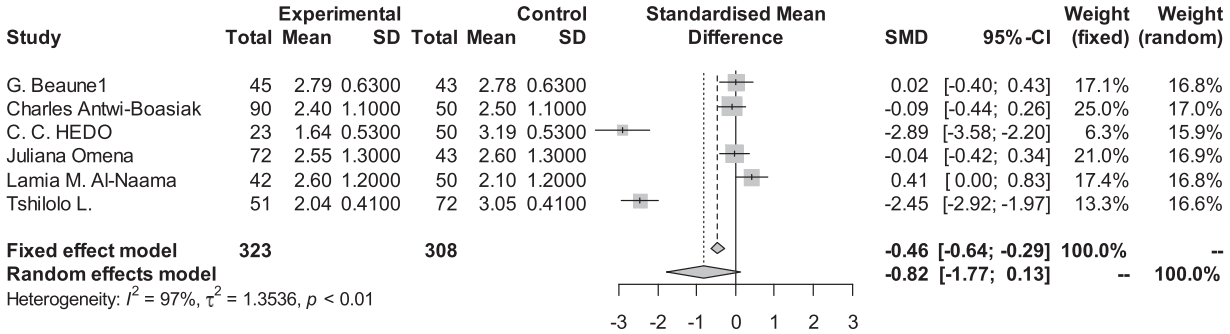

FIGURE 5 Serum transferrin from included studies.

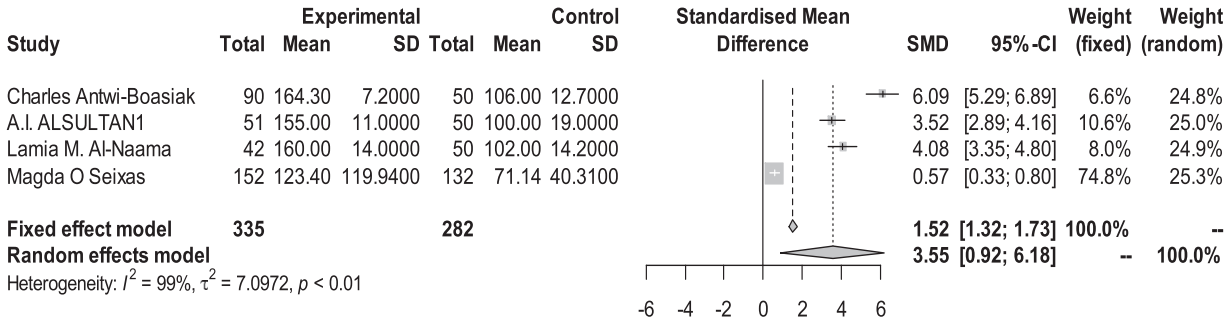

FIGURE 6 Serum iron from included studies.

3.6 | Transferrin, sickle cell anemia against the control

Six of the included case-control studies described transferrin in the study population for a study population size of 323 for cases and 308 for controls. The SMD obtained with a fixed model effect for all the 06 studies is −0.46, thus, it shows the weak influence of sickle cell anemia and tranferrin compared to the control population with [95% CI: (−0.64 to 0.29); (p < 0.01)]. The study with the largest SMD is that of Lamia et al.[46] with 0.41 [95% CI: 0.00; 0.83] (Figure 5).

3.7 | Serum iron, sickle cell anemia versus control

Four of the included case-control studies described serum iron in the study population for a study population size of 335 for cases and 282 for controls. The difference in standardized mean obtained with a fixed model effect in these studies is 1.52, thus reflecting the significant extent of sickle cell disease on serum iron compared to the control population with [95% CI: 1.32–1.76; (p < 0.01)]. The study that showed greater SMD is that of Charles Antwi-Boasiak et al.[28] with 6.09 [95% CI: 5.29–6.89]; the one with the lowest SMD is that of Seixas et al.[36] with 0.57 [95% CI: 0.33–0.80] (Figure 6).

4 | DISCUSSION

We have found that sickle cell anemia is significantly associated with significantly higher levels of ferritin, serum iron and CRP compared to the normal population. The risk of iron accumulation is greater in patients with homozygous (SS) sickle cell disease than in healthy (AA) subjects. This meta-analysis describes the iron balance disorders in sickle cell patients in inflammation in world in general, and Africa in particular. Studies analyzing markers of iron balance have been included in the selection, but particular emphasis has been placed on the most commonly studied ferric and inflammatory markers due to their accessibility; including ferritin, serum iron, transferrin and CRP. Iron is an essential molecule for hematopoiesis: 75% of the iron present in the body is used for the synthesis of hemoglobin.[48] Iron comes from two sources: first from the destruction of old red blood cells and secondly from food. Dietary iron is absorbed by the duodenum under the control of a protein synthesized by the liver, a true hyposideremic hormone, hepcidin which decreases the absorption of iron when there is too much iron by inhibiting the only exporting protein: ferroportin.[45] Ferritin is the cellular iron storage protein; found abundantly in the liver, spleen, bone marrow and macrophage.[35] It decreases in the event of iron deficiency and increases in the event of iron overload.[35] It is also a marker protein for inflammation.[48] Total iron-binding capacity is a measure of the maximum amount of iron that serum proteins can bind.[35] Transferrin is a glycoprotein made up of different isoforms that transport iron in plasma, between the gastrointestinal tract, iron storage organs such as the liver, spleen and bone marrow, and iron processing organs such as hematopoietic tissue. Its transferrin concentrations may thus indicate iron overload or deficiency.[35] CRP is a protein that appears in the blood during acute inflammatory processes. It is synthesized by the liver under the action of proinflammatory cytokines, and released into the blood at an early stage of the inflammatory reaction.[6]

Hemoglobin is the globular protein responsible for transporting respiratory gases. Ten of the included case-control studies described hemoglobin in the study population for a study population size of 854 for cases and 562 for controls. The fixed model effect SMD obtained for all 05 studies was −1.79 due to the mean difference in hemoglobin between the sickle cell population and the controls. Indeed, the general mean hemoglobin in the cases is 8 ± 2 g/dL and in the controls 13 ± 3 g/dL; consequence of SMD between the different included studies. Thus, it shows the weak influence of hemoglobin in the cases compared to the control population with (95% CI: −1.92 to −1.86; $p < 0.01$). The study with the largest SMD is that of Tshilolo et al. with −0.78 [95% CI: −1.16; −0.41].[22] Anemia during sickle cell anemia is the intrinsic consequence of hemolysis; which hemolysis associated with inflammation in the sickle cell patient are cause of iron profile disturbances.

Furthermore, studies described a significant increase in markers of inflammation (CRP, ferritin) in the cases compared to the control ($p < 0.001$) (Figure 3).[31,37] CRP is a protein that appears in the blood during acute inflammatory processes. It is synthesized by the liver under the action of proinflammatory cytokines, and released into the blood at an early stage of the inflammatory reaction.[6] The elevation of the CRP, therefore, suggests the role of this protein in activating inflammation in sickle cell patients. They have also described in sickle cell patients the association of the disease with other inflammatory parameters such as haptoglobin.[31] Indeed, intravascular hemolysis is described as causing a state of endothelial dysfunction, vascular proliferation, inflammation and oxidative stress. Several recent studies have demonstrated the roles played by free plasma Hb in reducing the effects of nitric oxide. Intravascular hemolysis associated with nitric oxide reduction cause overexpression of endothelin-1 responsible for the activation of endothelial adhesion molecules and platelets. Thus, nitric oxide not only causes vasoconstriction, but is also involved in endothelial activation and proliferation; the above actively contributes to the pathogenesis of SCA.[49–51] It is described that sickle cell red blood cells bind to the vascular endothelium cellular from alpha-4 integrin beta-1. This membrane protein then acts as a receptor for fibronectin and/or VCAM-1. In the endothelium, VCAM-1 is stimulated by inflammatory cytokines, including IL-6 and IL-8, which are released by the activated leukocytes. Heme and hemin, which are released in the circulation during the active phase of sickle cell disease, also contributes to inflammatory states in sickle cell patient because it promotes the increase in the expression of endothelial adhesion molecules and leukocyte adhesion and reticulocytes to endothelial cells.[52] Much more, inflammation is responsible for greater disturbances of the iron profile in SS patients compared to AA control, as reported by the included studies. As reported in the literature, hepcidin levels, a key modulator of iron metabolism, are influenced by erythropoiesis, iron, and inflammation, all of which can be increased in patients with major sickle cell syndromes.[25,43]

Indeed, the case-control studies described the influence of sickle cell disease on ferritin and iron balance[45] (Figure 4). Here, the authors described the relationship between markers of oxidative stress, ferritin, and insulin resistance in sickle cell patients and their corresponding controls. They obtained a significant increase in ferritin in the sera tested in SS sickle cell patients compared to normal AA controls ($p = 0.001$).[45] Indeed, ferritin is a biomarker of iron stores and can be used to detoxify excess iron. Thus, serum ferritin is used as the main exploration test during a suspected iron overload.[45] The increase in serum ferritin in sickle cell patients could be due to the following reasons: excess free iron, due to the excessive breakdown of hemoglobin and the abnormal circulation of the hemoglobin mass in the reticuloendothelial system which exert positive feedback on ferritin synthesis. Ferritin levels may be increased in response to oxidative stress resulting from excess reactive oxygen species manufacture.[45] In addition, elevated ferritin is a reflection of chronic inflammation.[8] Several authors also report high concentrations of serum iron and iron-containing compounds including heme and hemoglobin in the plasma of patients by hemolysis and blood transfusions.[53] And it is described that inflammation is one of the factors likely to increase and vary plasma Interleukin 6 concentrations. Studies have shown the elevation of proinflammatory cytokines including tumor necrosis factor-α, interleukin (IL)-6, and IL-17 during inflammatory processes in sickle cell

patients, including vasooclusive crises, hemolytic processes, and activation of endothelial cells in sickle cell disease.[35,54,55]

However, the study with the lowest SMD was that of Tshilolo et al.[22] with 1.31 (95% CI: 0.92; 1.71) still showing the significant extent of sickle cell disease on the iron profile in general and ferritin in particular. Here, the authors described the iron status in 72 homozygous Congolese sickle cell disease patients. The iron state was evaluated from a profile including several parameters namely transferrin, ferritin, total iron binding capacity, blood count, and transferrin saturation coefficient, as well as CRP. The means of the values obtained were compared with those of a non-sickle cell control group matched in age and sex. The authors described a significant increase in serum ferritin compared to the control population correlated with a significant increase in CRP ($p < 0.01$).[22]

Concerning serum iron, the included studies generally described a significant elevation of serum iron compared to the normal population ($p < 0.001$) (Figure 6). They have shown an association of disturbances in the iron balance with a significant drop in hemoglobin level ($p < 0.001$).[28] In fact, serum iron, which actively contributes to oxidative stress, is significantly elevated in sickle cell patients compared to the normal population. This observation is also described by several authors.[44,46,55] Iron is a powerful prooxidant which converts hydrogen peroxide into free radicals. The resulting free radicals cause cellular oxidation by destroying lipids, proteins and DNA.[46] The significant rise in serum iron in sickle cell patients in a vaso-occlusive crisis is in part the result of a rapid autooxidation of hemoglobin at the origin of the intravascular hemolysis observed in sickle cell patients, the cause of hyper inflammation in this last. The study with the lowest SMD was that of Seixas et al.[36] with 0.57 [95% CI: 0.33; 0.80] thus showing a moderate influence of sickle cell disease on serum iron in sickle cell patients. They also showed a significant elevation of serum iron in sickle cell patients compared to the normal population ($p < 0.001$).

Concerning transferrin (Figure 5), during sickle cell disease, the high frequency of hemolysis is accompanied by a decrease in serum transferrin whose capacities are exceeded at the origin of its decrease as reported by the authors of the included studies.[25]

In short, these data highlight the need to prevent inflammation in sickle cell patients, as they are a risk factor for the elevation of serum iron, which constitutes an important pro-oxidant, and causes high oxidative stress and cardiovascular disease.

5 | CONCLUSION

This review article indicates that people with sickle cell disease, especially homozygotes, have a high frequency of inflammation. The mechanisms involved in inflammation constitute risk factors for an iron profile disorder mainly marked by an increase in ferritin and serum iron, thus predisposing sickle cell patients to high oxidative stress and therefore to cardiovascular disease.

AUTHOR CONTRIBUTIONS

Romaric Tuono De Manfouo: conceptualization; data curation; formal analysis; investigation; methodology; writing—original draft; writing—review & editing. **Josué Simo Louokdom**: formal analysis. **Bernard Claude Chetcha**: methodology. **Prosper Cabral Biapa Nya**: validation; visualization. **Constant Anatole Pieme**: methodology; validation. **Claude Tayou Tagny**: methodology; supervision; validation.

ACKNOWLEDGMENTS

We address our sincere thanks to all the laboratory staff of Faculty of Medicine and Biomedical Sciences of *Université de Yaoundé I* and *Université des Montagnes* for their help in carrying out this work.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data used to support the findings of this study are available from the corresponding author upon request. The authors confirm that the data supporting the findings of this study are available within the article [and/or] its Supporting Information Materials.

TRANSPARENCY STATEMENT

The lead author Romaric Tuono De Manfouo affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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How to cite this article: Tuono De Manfouo R, Louokdom JS, Chetcha BC, Nya PCB, Pieme CA, Tagny CT. Homozygote drepanocytosis: ferric status and inflammation in world and Africa: review article and meta analysis. *Health Sci Rep*. 2023;6:e1609. doi:10.1002/hsr2.1609