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Does Sickle Cell Disease Protect against HIV Infection: A Systematic Review

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Highlights of the Study

- Recurrent blood transfusion is a primary mode of management of many complications of sickle cell disease.
- Human immunodeficiency virus (HIV) is transmitted via blood transfusion, but its prevalence among patients with sickle cell disease is lower than in the general population.
- Autosplenectomy has been proposed as a mechanism for the reduction of virulence of HIV in sickle cell disease patients.

Keywords
Sickle cell disease · Human immunodeficiency virus

Abstract

Objective: The aim of this systematic review was to investigate whether sickle cell disease (SCD) protects against human immunodeficiency virus (HIV) infection by determining the association between SCD and the incidence and virulence of HIV infection. ***Methods:*** This is a systematic review that used MEDLINE, PubMed, CINAHL, and Academic Search Complete as data sources. Articles describing the relationship of SCD with HIV infection were included in this review. The effect measures were converted to correlation coefficients and synthesized accordingly to examine the putative protective role of SCD against HIV infection. Independent full-text screening and data extraction were conducted on all eligible studies. The risk of bias was assessed using the mixed methods appraisal tool. We employed a random-effects model of meta-analysis to estimate the pooled prevalence. We computed Cochrane's Q statistics, I^2, and prediction interval to quantify effect size heterogeneity. ***Results:*** SCD reduces the risk of HIV infection by 75% (odds ratio [OR] = 0.25; $r = -0.36$, $p < 0.001$; $I^2 = 71.65$). There was no publication bias (Egger's t value = 0.411; $p = 0.721$). Similarly, risk of HIV virulence was reduced by 77% (OR = 0.23; $r = -0.38$; $p < 0.001$; $I^2 = 63.07$). The mechanisms implicated in the protective influence of SCD include autosplenectomy, reduced CCR5 expression, and increased expression of heme and iron-regulated genes. ***Conclusions:*** SCD appears to protect against HIV infection and slows HIV progression.

Introduction

Global distributions of sickle cell disease (SCD) and human immunodeficiency virus (HIV) intersect, with Africa serving as the center for both diseases [1, 2]. The presence of hemoglobin SS (HbSS) and other structurally

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aberrant hemoglobin S variants (HbSC, HbC, HbS/β thalassemia, and combinations with other β chain variants) characterize SCD, a severe genetic illness [3]. SCD is characterized by vascular occlusions leading to anemia, ischemia damage to tissues, increased rate of hemolysis, and increased susceptibility to infection due to immune compromise [3]. HIV, on the other hand, exploits white cell surface proteins, leading to lytic destruction, $CD4^+$ T cell lymphopenia, and immunosuppression [4]. HIV-infected individuals frequently suffer from a wide range of health complications, some of which are directly related to the disease condition, while others are due to aging, antiretroviral therapy, or other patient factors. Life expectancy for patients with HIV [5] and SCD [6] has improved significantly over the past three decades because of new diagnostic methods as well as improved treatment options. In developed countries, both disease conditions have become long-term illnesses. An estimated 300,000–400,000 newborns globally are born every year with SCD, with the majority (about 75%) occurring in Sub-Saharan Africa [7]. It is estimated that nearly 90,000 people in the USA have SCD, the majority of whom are African American [8]. According to the 2018 estimates from the World Health Organization, the global HIV infection of approximately 36.9 million people had its concentration in Africa [9]. Sub-Saharan Africa is home to a staggering 64% of the world's HIV-infected adults, 91% of its infected children under the age of 15 years, and about 10–40% of the world's SCD population [1, 10].

With limited treatment options, both diseases have high morbidity and mortality rates. However, the prevalence and progression of HIV in individuals with SCD are significantly lower than in the general population as reported in several studies [11–14]. As early as in the 1980s and 1990s, researchers began to speculate that SS disease may have a positive impact on the natural course of HIV type 1 (HIV-1) disease [15, 16]. It has been suggested that just as sickle cell trait protects against malaria, it may protect against HIV infection as well, by altering CXCR4 and CCR5 receptors on $CD4^+$ T cells, thereby preventing viral entrance and infection [10]. CCR5 and CXCR4 are chemokine receptors involved in the regulation of cell migration during inflammation and in immunity [17]. They function as co-receptors for the entry of HIV-1 into immune cells. CCR5 and CXCR4 are utilized by viruses for entry into cells during the early and late stages of viral infection, respectively. Presently, these co-receptors are being targeted for control of HIV infection and disease progression [18].

Host variables may play a role in the delay or absence of clinical symptoms of HIV. The absence of a key location for HIV virus invasion and replication, such as the lymph nodes or the spleen, may be a factor in the reduced virulence [19, 20]. Micro-infarction is the primary cause of functional asplenia in about 95% of people with HbSS [21]. Heme and iron regulation mechanisms in SCD, as well as mild hemolysis, have all been implicated in limiting HIV-1 infection [22].

Patients with SCD have equally been found to have lower rates of HIV-related death and progression to AIDS than the general population [20, 23, 24]. However, the outcomes of investigations on the possible implications of SCD-HIV comorbidity have been inconsistent. According to Neto et al. [25], HIV infection had no correlation with SCD symptoms; however, a study found that SCD patients had a slower progression of HIV infection into AIDS than their non-SCD counterparts [26]. Another study showed that SCD patients with HIV face a higher risk of developing SCD complications, despite the fact that it may slow HIV progression and mortality [27]. Children with SCD and HIV were more likely to suffer from bacterial infections and sepsis than those with SCD alone, and their hospital stays were longer than those without (8.0 days vs. 4.3 days, respectively) [28]. The public health significance of both diseases emphasizes the necessity to re-examine previously published findings on how one disease impacts the other. In this review, we aimed to provide a systematic review of the interaction between SCD and HIV infection and the degree of protection against HIV conferred by SCD. This study aimed at ascertaining whether SCD protects against HIV infection by determining the association between SCD and the incidence and virulence of HIV infection.

Materials and Methods

Design

This is a systematic review of observational studies. The protocol was structured in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline [29].

Study Characteristics

This review included all peer-reviewed English literature, regardless of location, sample size, or test statistics. Participants: individuals diagnosed with SCD and/or HIV. Studies were included regardless of whether or not hematological confounding variables were examined. The intervention was not applicable as this was a systematic review of observational studies that examined the protective effects of SCD on HIV. Studies were included regardless of whether or not a control group was used to study the subject. We included only studies that explored the protective effects of SCD on HIV.

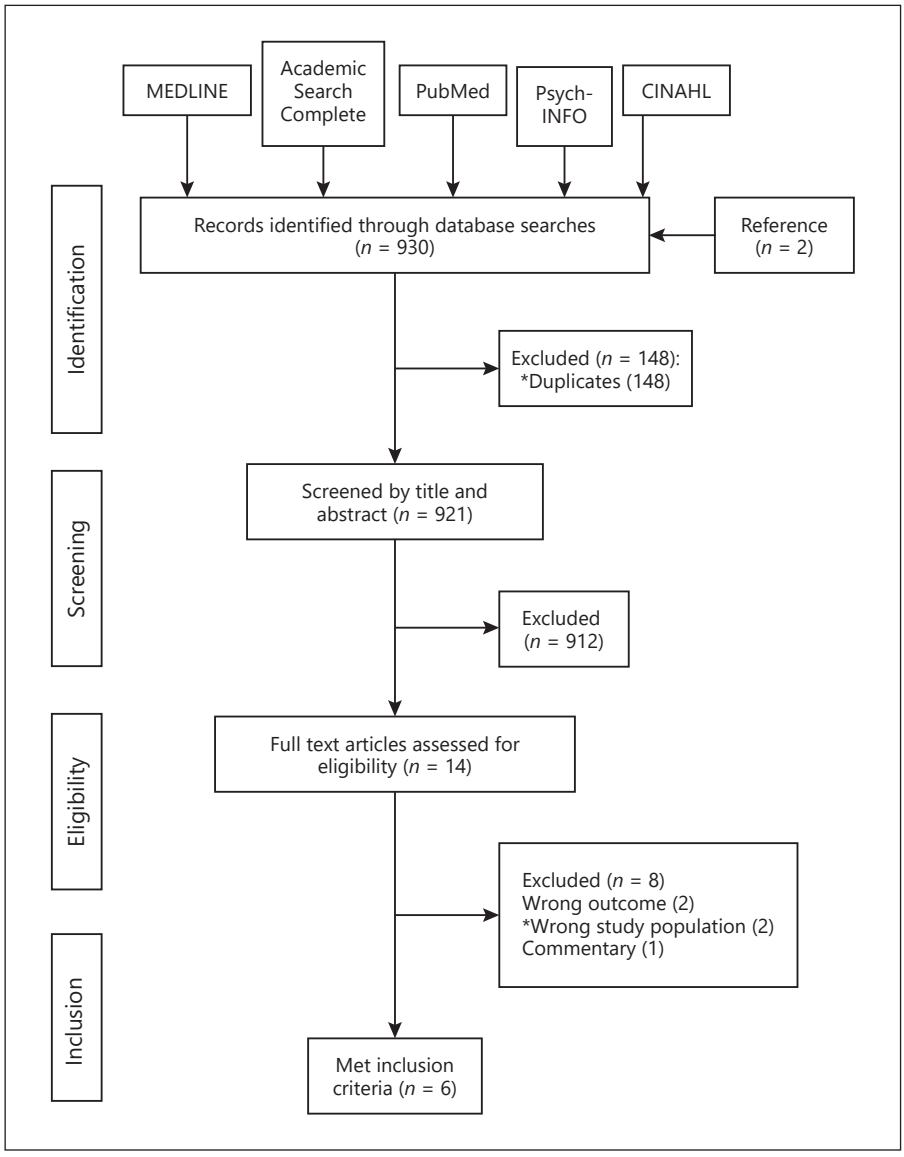

Fig. 1. PRISMA flow for study inclusion and exclusion. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Eligibility Criteria

Inclusion criteria were peer-reviewed articles reporting the relationship of SCD or trait with HIV, peer-reviewed articles published in English, and studies in which estimation of outcome variables was done using standard methods. Exclusion criteria were studies published in a language other than English, studies in which estimation of outcome variables was done using substandard methods, and gray literature and opinion papers.

Information Sources and Search Strategy

PubMed, MEDLINE, CINAHL, and Academic Search Complete were searched using medical subject headings (MeSH) and keywords identified in the title, abstract, and/or text of the articles. PubMed was used to test the search strategy. MeSH terms identified using Cochrane MeSH terms were included in the pilot search. After exploring various combinations of these terms, the most sensitive strategy was chosen and reported. Sensitivity judgments were made at face value. The strategy was modified to accommodate the syntax and subject headings of the remaining databases (MEDLINE, CINAHL, and Academic Search Complete). The reference lists of selected papers and reviews were combed to identify potentially relevant studies.

Study Records and Data Management

The results of the literature search were exported directly from databases into EndNote 8 (Clarivate, Philadelphia, PA, USA), where they were de-duplicated and screened. Following the initial screening, two research assistants independently screened the bibliographic records exported to COVIDENCE Veritas Health Innovation Ltd., Melbourne, VIC, Australia (Extraction 2). We used a piloted and updated screening template, which contains questions about eligibility, to assist with the screening process.

Table 1. Sociodemographic characteristics

ID/Authors	Age	Female, %	Design	Sample size	Sample tech	Country	Setting
Castro et al. [35]	30.3 (–)	49.14	Prospective	116	Non-p	USA	Blood banks
Kelly et al. [36]	39.2 (23–58)	44.4	Retrospective Prospective	274	Non-p	USA	Community Hospital & Blood center
Kumari et al. [37]	–	–	Cross-sectional	45	Non-p	USA	Clinic
Nouraie et al. [12]	31 (25–40)	61.5	Retrospective	6,517	Non-p	USA	National hospital
Bagasra et al. [20]	–	36	Cross-sectional	36	Non-p	USA	SCD centers
Ssenyondwa et al. [38]	3.6±3.9	39	Retrospective	130	Non-p	Uganda	HIV clinic

Selection Process

An expert reviewer conducted a first screening of the title and abstract to identify those that met the inclusion criteria. Following that, two research assistants conducted an independent screening. In consultation with the expert reviewer, conflicts were resolved to agree on the articles to be included. One of the research assistants downloaded the full texts of the articles included. The two research assistants undertook independent screening of full texts and data extraction. Where necessary, emails were forwarded to authors of selected studies to clarify selection criteria-related issues. A Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram was used to illustrate the flow of studies throughout the selection process, as well as the reasons for exclusion shown in Figure 1.

Quality Appraisal and Risk of Bias Assessment

Quality appraisal was executed using Mixed Method Assessment Tool (MMAT) [30]. The MMAT examines the appropriateness of the aim of the study, adequacy and methodology, study design, participant recruitment, data collection, data analysis, presentation of findings, and authors' discussion and conclusions. There are 5 sections in this tool; section 1 is for qualitative study assessment, sections 2, 3 and 4 are used to assess quantitative studies, while section 5 is for studies with mixed methods. Section 4 is used for quantitative noninterventional descriptive studies, and thus, only section 4 was used in the analysis for this review. MMAT is valid, reliable, meets acceptable standards, and is suitable for the appraisal of most study designs [31]. Quality appraisal was executed by two reviewers. A random sample consisting of 20% of the eligible articles, with excellent inter-rater reliability was achieved. The remaining 80% was executed by one of the reviewers.

Data Items

Primary data sought were estimates of the relationship between SCD and HIV occurrence and virulence. Age and gender constitute secondary variables. Additionally, information gathered from each article included the authors' names, design, sample size, the sampling techniques, the country, and a summary of the findings. Consistent with Herbeck et al. [32], we defined HIV virulence as the rate of progression of HIV infection to AIDS. In this review, we measured virulence in terms of CD4 count and viral load.

Data Synthesis and Assessment of Heterogeneity

We quantified the magnitude and direction of the relationship of SCD with HIV infection through meta-analysis. Pooled correlation coefficient and odds ratio (OR) were estimated accordingly. We fitted meta-regression models to discover potential drivers of variability in the relationship of SCD with HIV infection. The contribution of each study characteristic to heterogeneity was quantified using OR as well as correlation coefficient [33, 34]. Comprehensive Meta-analysis software (Comprehensive Meta-analysis Version 3; Biostat, Englewood, NJ, USA) was used, with α set at 0.01. The heterogeneity measures, Cochrane's Q statistics, I^2, and prediction intervals were calculated following Higgins et al. [35]. I^2 values between 0 and 40% were interpreted as low heterogeneity, 30–60% as moderate heterogeneity, 50–90% as substantial heterogeneity, and 75–100% as considerable heterogeneity, according to the Cochrane Handbook for Systematic Reviews of Interventions [35].

Results

A total of 930 records were identified from databases and reference lists. Following de-duplication, we eliminated 146 records, leaving 921 articles for the title and abstract screening. Ultimately, six studies met the eligibility criteria and were included in the review shown in Figure 1. All six studies provided quantitative estimates of the relationship between SCD and HIV infection and were involved in the meta-analysis.

Sociodemographic Characteristics and Quality Appraisal

Two countries were represented in this review, of which, five (83.3%) of the studies were conducted in the USA. A total sample of 7,417 SCD patients was involved. The mean age of the study participants was 26.0 years, while the overall female percentage was 38.3% as shown in Table 1. Regarding the quality of the included studies, 3 (50%) possessed low risk, while 3 (50%) were of moderate risk of bias as shown in online supplementary Table 1 (see www.karger.com/doi/10.1159/000526993 for all online suppl. material).

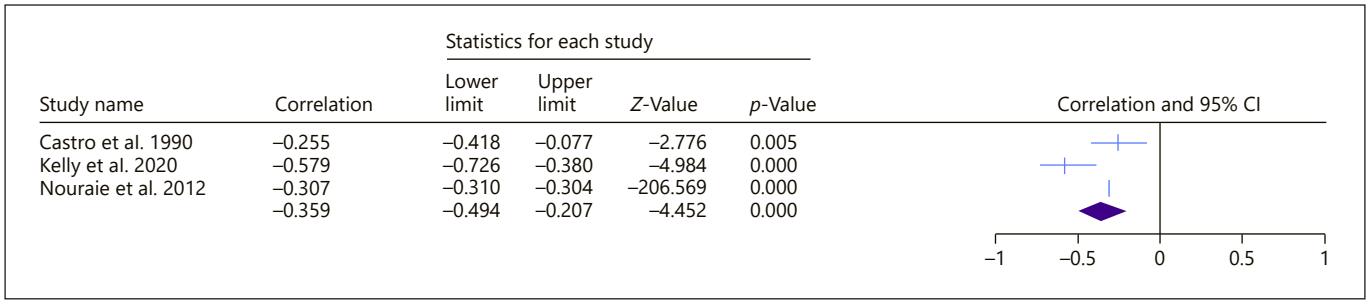

Fig. 2. Forest plot displaying the association between SCD and occurrence of HIV infection.

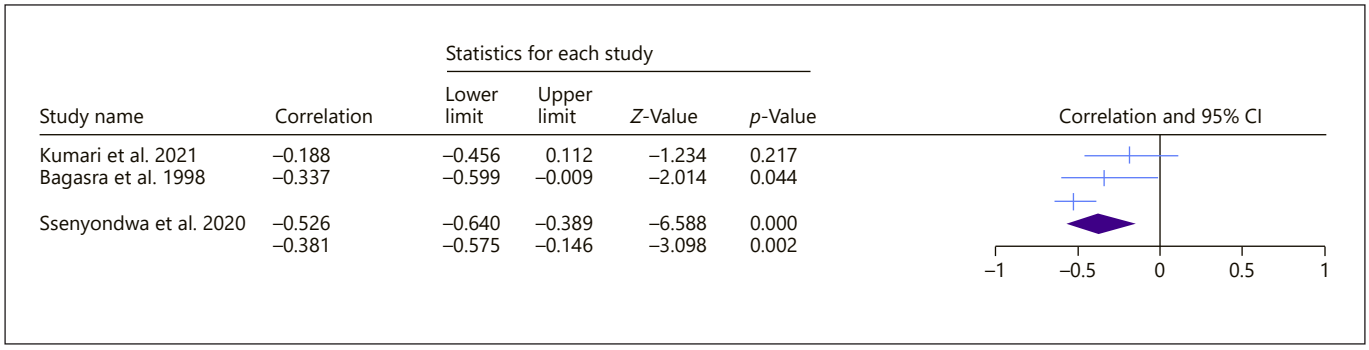

Fig. 3. Forest plot displaying the association between SCD and HIV viremia.

Relationship of SCD with HIV Infection

Six studies were included in this review (online suppl. Table 1). Of these, three reported a lower risk of HIV infection in sickle anemia patients, while three reported lower HIV virulence in sickle cell anemia patients (online suppl. Table 2). In the meta-analysis, we included the six studies that reported a measure of interaction between SCD and HIV infection. Result shows that SCD reduces the risk of HIV infection by 75% (OR = 0.25; $r = -0.36$, $p < 0.001$; $I^2 = 71.65$). There was no publication bias (Egger's t value = 0.6278; $p = 0.6431$) shown in Figure 2. Similarly, risk of HIV virulence was reduced by 77% (OR = 0.23; $r = -0.38$; $p < 0.001$; $I^2 = 63.07$). There was no publication bias (Egger's t value = 1.9902; $p = 0.2964$) shown in Figure 3. In the current review, the mechanisms implicated in the protection of SCD against HIV include autosplenectomy [20], enhanced immunological defense [12, 36, 37], and ferroportin as a trigger of HIV-1 restriction [22] as shown in online supplementary Table 2.

Discussion

SCD reduces the risk of HIV infection by 75%, while the risk of worsening HIV progression was reduced by 77%, according to our review. This is consistent with the findings of Owusu et al. [26]. SCD is hypothesized to have a protective effect against HIV infection by an enhanced immunological defense in which increased inflammation, iron metabolism, and immunologic alterations create an unfavorable environment for HIV replication [38, 39]. CCR5 is a chemokine receptor that, in addition to acting as an HIV co-receptor, modulates the action of inflammatory cells [40]. An allele of the CCR5 gene with a 32-base pair deletion in the coding region is labeled CCR532 which causes the absence of cell surface expression of CCR5 in homozygotes, which has been linked to immunity to HIV infection. CCR5 expression is usually lower in people who are CCR532 heterozygous [41]. In a case-control Brazilian study, 1.3% of healthy controls carried the CCR532 allele, while 5.1% of SCD patients had the allele, thus highlighting the association between CCR5Δ32 and SCD [42]. Macrophage-tropic

HIV-1 infections can be suppressed by this CCR532 allele [42].

The absence of a spleen, also known as autosplenectomy, has been linked to immunological alterations in SCD patients [20]. Splenic sequestration, in which large volumes of blood collect in the spleen but do not flow through the vasculature, is a well-known consequence of SCD-induced ischemia. The spleen may atrophy as a result of recurrent ischemia and infarction, which may lead to autosplenectomy [43]. The lack of a functional spleen, which is a significant location for HIV infection and proliferation, is one reason for the low virulence [20]. There seems to be a paradoxical relationship between autosplenectomy and susceptibility to infection. While this phenomenon appears to lower the virulence of HIV among patients with SCD, it is a cause of overwhelming sepsis, especially among children with SCD who have bacterial infections. Thus, autosplenectomy may account for the long-term lack of progression of HIV-1 in infected SCD patients [18], on the one hand, and a susceptibility to sepsis from bacterial infections, on the other hand [44].

Concerning iron metabolism, Kumari et al. [38] observed a low incidence of HIV-1 infection in individuals with SCD, as well as inhibition of HIV-1 replication in vitro in the presence of low intracellular iron or heme therapy. This finding indicates a possible protective role of SCD from HIV infection. Kumari et al. [38] observed that HIV-1 replication was suppressed in ex vivo infection of SCD peripheral blood mononuclear cells via mechanisms involving the induction of heme oxygenase-1 (HO-1). The increased expression of heme and iron-regulated genes, such as ferroportin, IKBα, HO-1, p21, and SAM domain and HD domain-containing protein 1 (SAMHD1), has been shown to restrict HIV-1 infection in patients with SCD [45]. Furthermore, iron chelators were also found to suppress HIV-1 infection, buttressing the important role of iron homeostasis in the pathogenesis of HIV-1 [36]. Iron chelators have been shown to promote the expression of P21 which is an inhibitor of cyclin-dependent kinase-2 (CDK2). Cyclin-dependent kinase 2 is a protein kinase, the activity of which is limited to G1-S phase of the cell cycle. Inhibition of CDK2 leads to inhibition of cell growth [46].

In terms of HIV virulence, SCD reduces the HIV virulence by 73%. Nouraie et al. [12] reported a decreased rate of HIV comorbidity in African Americans with SCD who were discharged from the hospital [12]. The rationale for this is that in people with SCD, there is a natural and significant control of collapsing focal segmental glomerulosclerosis and proteinuria, which is typical of HIV-1-associated nephropathy and occurs in tandem with HIV-1 progression [47]. Even though SCD appears to protect against HIV co-infection and morbidity, it is important to note that HIV can aggravate SCD [23]. Hemoglobin SC patients with HIV were shown to have abnormally high levels of intra- and extraerythrocytic crystals (resembling the case of hemoglobin C, but not to such extreme levels) which were linked to HIV infection [48]. Hence, it appears that while HbSS is protective of HIV infection, HbSC facilitates HIV progression among SCD patients with HIV.

Conclusion

SCD appears to confer some protection against HIV infection as well as reduce HIV virulence.

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Statement of Ethics

An ethics statement is not applicable because this study is based exclusively on published literature.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Theresa Ukamaka Nwagha and Angela Ogechukwu Ugwu conceptualized the study which was designed by Martin Nweke with input from Theresa Ukamaka Nwagha and Angela Ogechukwu Ugwu. All authors contributed to screening and extraction of data. The initial draft was written by Martin Nweke. All authors revised the manuscript and approved the final version.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author.

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