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REVIEW

Impact of Sickle Cell Disease on Affected Individuals in Nigeria: A Critical Review

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Abstract: Sickle cell disease is an autosomal recessive disorder of the beta-globin gene, with resultant deformation of the red blood cells and variable clinical outcomes. Nigeria is recognised as the country with the highest burden of sickle cell disease globally. This study aimed at critically reviewing available literature on impact of sickle cell disease in Nigeria. A literature search was carried out on four databases, and a total of 116 articles that met the inclusion criteria were included in the critical review. It was observed that majority of the studies were carried out in South-Western part of Nigeria (47.4%), whilst the North-East had the least number of studies undertaken in this area, more than a quarter of the studies (27.6%) were related to hematologic and serologic screening. Major themes that emerged from this review were morbidity and mortality; prevalence of sickle cell disease; issues relating to blood transfusion; psychosocial impact; and anatomical dysfunction in sickle cell disease. Intervention programs from both government and non-governmental organizations aimed at reducing the burden of sickle cell disease and its socio-economic impact were identified as key to strategies aimed at overcoming challenges associated with the disease. Findings from this study also revealed that education and awareness interventions were central to reducing the prevalence of sickle cell disease in this setting.

Keywords: sickle cell anemia, public health, hematology, genotype, hemoglogin, gene, red blood cell, vaso-occlusive crises

Introduction

Sickle cell disease is an autosomal recessive genetic disorder which occurs as a result of mutated beta-globin gene inherited from both parents.[1,2] Hemoglobin SS genotype (Hb SS) is the most common type of sickle cell disease.[3] Other familiar sickle cell genotypes include sickle hemoglobin C disease (Hb SC) and the beta thalassemia (Hb Sb° and Sb+). Rare variants such as hemoglobin SE, hemoglobin SD Los Angeles, and hemoglobin SG-Philadelphia have also been identified.[4,5] Fully functional beta-globin arises from the normal wild-type allele of the β- globin gene (HbA). Over 400 mutant alleles have been identified and are known to give rise to variant hemoglobin or thalassemia.[6] Out of these, the allele for sickle cell disease has attracted the greatest attention because of its frequency and the severity of sickle cell disease.[7]

The basic pathophysiology of sickle cell disease involves the de-oxygenation and polymerization of red blood cells, leading to deformation and hemolysis. This therefore gives rise to varieties of clinical manifestations such as acute pain episodes and anemia.[8] The hallmark of sickle cell disease is vaso-occlusive crises, and it is the most common reason for frequent hospital visits for persons affected with the disease.[9]

Sickle cell disease has been recognized by the United Nations General Assembly as a disease of global public health concern. It is noteworthy that 20 to 25 million people are affected with sickle cell disease globally, out of which between 12 to 15 million reside in Africa, whilst developed countries only account for 10% cases.[10] Sub-Saharan Africa accounts for the highest percentages of various indices associated with sickle cell disorder. It accommodates 75% of all patients with sickle cell disease and 70% of all sickle cell disease births globally, with some of the affected children dying before the age of 5 years.[11] Nigeria is believed to be the most sickle cell endemic country in sub-Saharan Africa with between 2% and 3% of the total population affected.[12] This study aimed at critically reviewing the impact of sickle cell disease in Nigeria, alongside relevant

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emergent issues. The critical review strategy can help assess the impact of sickle cell disease holistically and provide policy direction for government in improving the quality of care for individuals with the condition.

Methods

Data Sources and Search Strategy

A detailed literature search was undertaken to identify publications that focused on sickle cell disease in Nigeria. Relevant articles were searched, screened, and included in this study accordingly. Articles were searched through Web of Science, PubMed, Google Scholar, and African Journal Online using different combinations of keywords which includes "sickle cell disease", "sickle cell anemia", "Nigeria" "burden" and "impact". All the four databases were carefully searched for only English-language full-text original articles published. Titles and abstracts of the retrieved documents were examined to identify those that were within the area of focus.

Review Selection

After the exclusion of duplicate literature, titles and abstracts of selected articles were carefully reviewed. All relevant full-text studies obtained were assessed for eligibility. Original articles from peer-reviewed scientific journals with primary data on various areas that focused on the impact of sickle cell disease in Nigeria were considered potentially eligible for inclusion in this review. All studies outside Nigeria were excluded.

Data Extraction and Analysis

Data were extracted from the selected studies into an Excel spreadsheet (Microsoft Office Excel 2013). The variables registered for each article were author, year of publication, name of the journal, and article title. Others include area of focus, geopolitical zone, method of data collection and age range of subjects. Data were then imported into Statistical Package for Social Sciences software version 25 for descriptive analysis, and results were summarized as figures.

Results

The literature search undertaken across various databases yielded 4812 articles that were related to sickle cell disease in Nigeria, and this covers between 1985 to 2021. After the elimination of duplicates, a total of 621 were retained. Following titles and abstracts screening, up to 178 full-text articles were eligible for consideration. Finally, a total number of 116 full-text articles (See Supplementary Table 1) which met the inclusion criteria were selected for critical review.[1,3–9,11,13–118] Further details on the search strategy are presented in Figure 1.

Bibliometry

Sickle Cell Disease Studies by Geopolitical Zone

Figure 2 shows the various geopolitical zones with their respective percentage of studies on sickle cell disease in Nigeria. It was observed that a considerable proportion of the studies (55; 47.4%) were carried out in the South-West zone. A total of ten studies were carried out each in North-Central, North-West, and South-South, whilst 20 studies were recorded in South-East.

Findings in Figure 2 show that studies encompassing all the zones were relatively few as only two (1.7%) of the articles in this review captured all six geopolitical zones in their data collection process.

Sickle Cell Disease Studies by the Method of Data Collection

Figure 3 gives a graphical illustration of sickle cell disease studies by the method of data collection. It was observed that data from laboratory tests dominated under this category (49; 42.2%).

Findings in Figure 3 indicate that only one of the articles' data collection process was underpinned by the use of interview. Studies involving questionnaires were of similar proportion with those that employed clinical investigation as their data collection strategy.

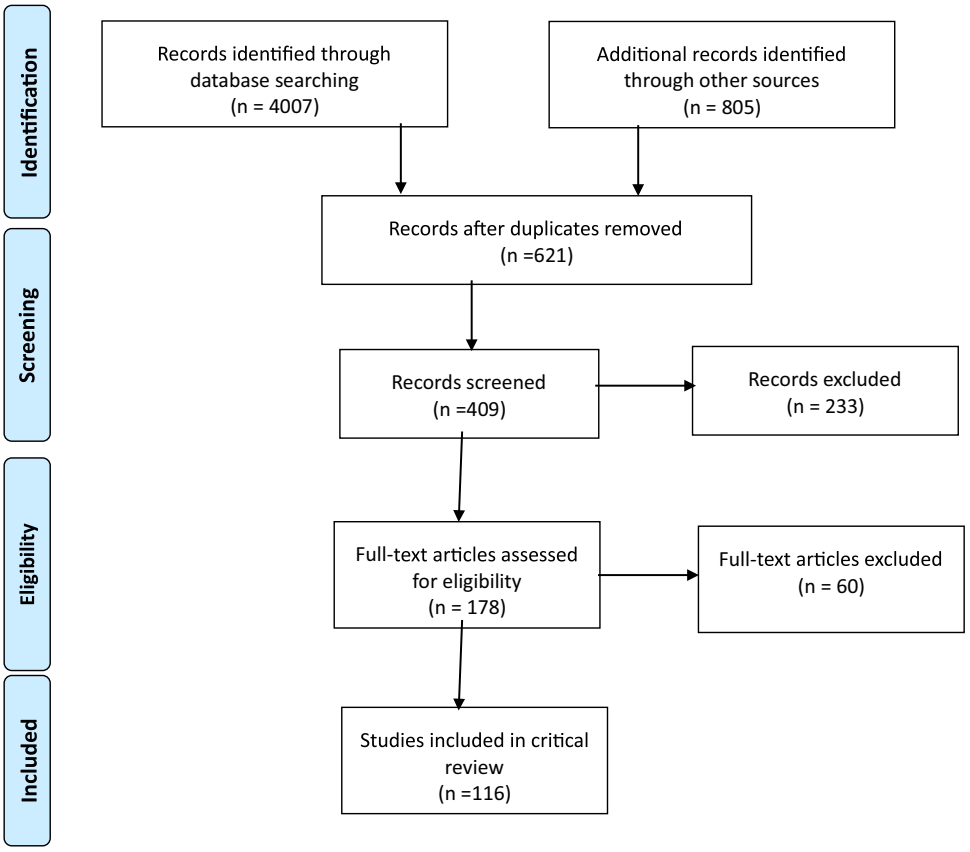

Figure 1 Review flow chart.

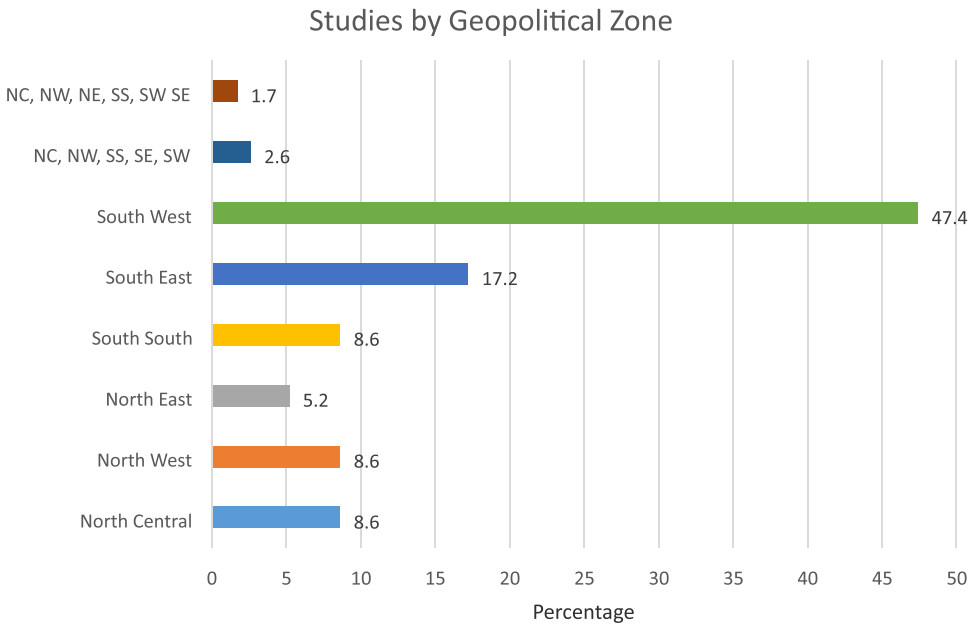

Figure 2 Articles according to geopolitical zone.
Abbreviations: NC, North Central; NW, North West; NE, North East; SS, South South; SW, South West; SE, South East.

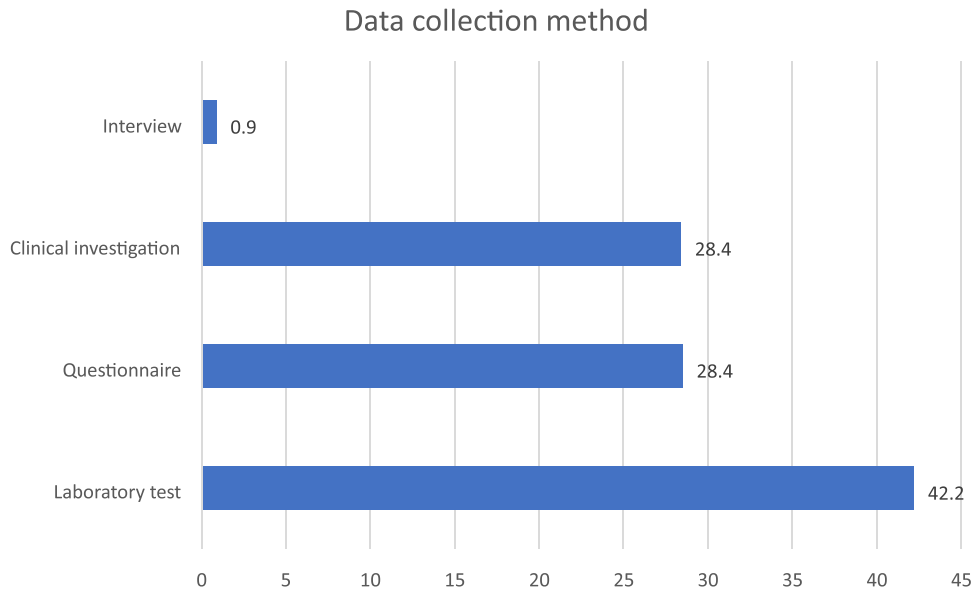

Figure 3 Sickle cell disease studies according to method of data collection.

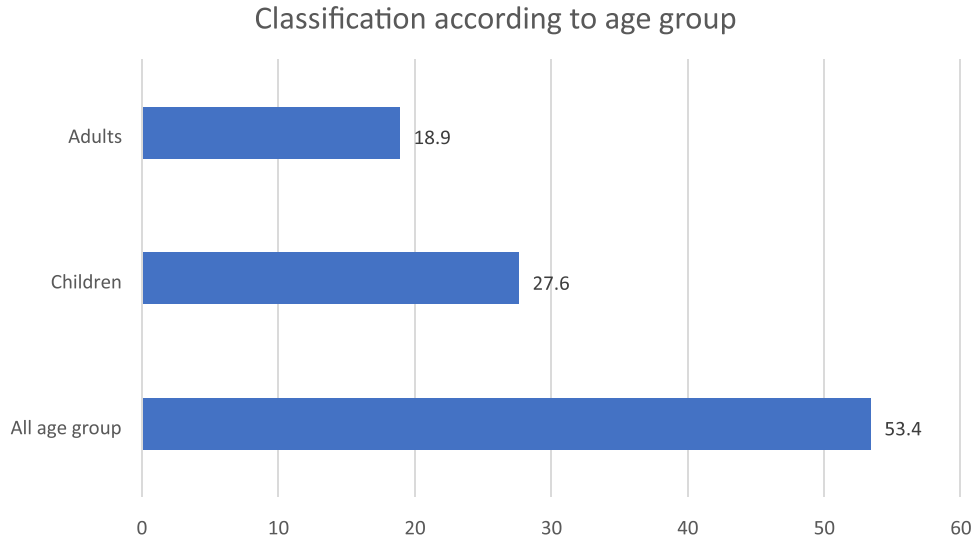

Figure 4 Classification according to age group.

Sickle Cell Disease According to Age Group

All articles evaluated were classified according to three age groups which include adults, children, and all age groups. The studies in the category of "all age group" were those that targeted both adults and children, and findings in Figure 4 show that majority of the articles reviewed (62; 53.4%) fell under this category.

Child mortality from sickle cell disease is high in Nigeria, and this has contributed to a substantial portion of the Country's under 5 years mortality over the years. Findings in Figure 4, however, show that slightly above a quarter of the studies (32; 27.6%) were undertaken among children.

Data Driven Thematic Explorations of Sickle Cell Disease

Cardiovascular Effect of Sickle Cell Disease

Various articles in this review focused on the cardiovascular effect of sickle cell anemia. Oguanobi et al reported a marked increase in pulse rate and pulse pressure with a decrease in diastolic blood pressure and mean arterial blood

pressure among patients with sickle cell disease.[13] Lower diastolic blood pressure and increased pulse pressure have been attributed to hemodynamic circulation in chronic anemia.[14] Sokunbi et al recommended cardiovascular examination for signs of pulmonary hypertension for children with sickle cell anemia due to increased risk of pulmonary hypertension.[15] Furthermore, pulmonary dysfunction has been observed among adolescents and adults with sickle cell disease in Nigeria. This was also attributed to raised white blood cells, leading to a cascade of inflammatory events.[16] VanderJagt et al suggested early nutritional intervention for children with sickle cell disease owing to reduced pulmonary function highlighted in their study.[17]

Heart rate variability and electrocardiogram reports had also been investigated among sickle cell disease patients. Adebiyi et al reported a reduction in heart rate variability among patients with vaso-occlusive crises.[18] Significant electrocardiographic abnormalities were also reported among patients with sickle cell disease.[19,20]

Morbidity and Mortality in Sickle Cell Disease

Findings by Akingbola et al revealed varying degree of abdominal pain among sickle cell disease patients with multifactorial etiology.[21] Some identified factors responsible for abdominal pain include retroperitoneal lymph node enlargement, bone marrow hyperplasia, hepatobiliary disease, splenic disorders, and mesenteric arterial thrombosis.[22,119]

Mortality in sickle cell anemia patients was linked to bacterial infection, necessitating the need for proper treatment with appropriate antibiotics.[23] Some bacteria commonly associated with mortality in sickle cell anemia include *Streptococcus pneumonia*, Salmonella species, and *Hemophilus influenza*.[24,120]

Effect of sickle cell disease on pregnant women had also been explored; Afolabi et al reported high maternal mortality in women with HbSS.[25] Ugboma and George highlighted malaria and vaso-occlusive crisis as the most common complications encountered in pregnancy.[26] Other relevant issues and complications documented include emergency cesarean section, low birth weight, and fetal mortality.[27]

Pattern of Sickle Cell Disease

Several studies explored the prevalence and pattern of sickle cell disease in Nigeria. Taiwo et al reported a prevalence of 2.4% for HbSS genotype in South-Western Nigeria.[7] Similarly, Stephen et al reported a gradual increase in the prevalence rate of sickle cell disease in Jos, Nigeria, in 2013 and 2014.[11] On the contrary, the case fatality rate for sickle cell disease gradually decreased from 15.4% in 2012 to 11.1% in 2013 and 10.3% in 2014. Other researchers that studied children in North Central Nigeria identified 5% prevalence rate of sickle cell disease among the study population.[28] However, Kingsley et al revealed a decline in prevalence of sickle cell disease from 2011 with the least prevalence reported in the years 2016 and 2017.[29]

Hematological and Serological Screening

Some studies reported a marked decrease in hemoglobin concentration and packed cell volume among patients with sickle cell disease.[30–32] Decreased mean cell hemoglobin and mean cell volume had also been reported among people with this condition.[33] Low serum zinc levels as well as increased copper levels were prominent among patients with sickle cell disease.[34]

A study among children affected with sickle cell disease revealed a decrease in Myeloperoxidase and Malondialdehyde.[35] In a study undertaken by Akinbami et al, it was observed that serum ferritin was higher in males than females.[36] Similarly, Odunlade et al reported increased serum ferritin levels among patients with sickle cell disease and this was attributed to iron overload.[37]

Studies on analysis of electrolyte activities and kidney function among sickle cell disease patients also revealed a marked decrease in sodium, potassium, creatinine, and urea, and this was indicative of chronic kidney disease.[8,38] Additionally, increased levels of alkaline phosphatase had been noted among people with sickle cell, and this was believed to be associated with vaso-occlusive crises involving the bones.[90]

Sickle Cell Disease and Blood Transfusion

The chances of acquiring infections are higher when blood is not properly screened prior to transfusion. Also, evidence suggests that blood transfusion services in some public hospitals had fallen short of best practices.[39] There were reported cases of human immunodeficiency virus infections following blood transfusion among patients with sickle cell disease.[40]

Blood transfusion was identified as a significant risk factor for the development of post-transfusion hepatitis in sickle cell anemia.[41–45] Furthermore, complications of red cell alloimmunization in multi-transfused patients with sickle cell anemia had also been highlighted as major challenges of blood transfusion in patients with sickle cell disease.[46,47,121]

Psychosocial Impact of Sickle Cell Disease

Interaction between patients, their disease condition, and social environment can lead to maladjustment which could provoke psychosocial dysfunctions.[48] Previous studies had reported cases of psychosocial problems in children suffering from sickle cell anemia, as well as their caregivers, and it was suggested that psychosocial management should focus more on families rather than affected individuals.[49,50] Available evidence also suggests that family members of patients with sickle cell disease suffer considerable financial, interpersonal, and psychological challenges due to the high cost of living up with sickle cell disease.[48] Previous findings, however, indicate that such challenges can significantly be reduced by external financial support from both government and non-governmental organizations.[51,52]

Anatomical Dysfunction in Sickle Cell Disease

Varying degrees of anatomical dysfunctions are reportedly associated with sickle cell disease. Nwadiaro et al identified *Staphylococcus aureus* as the leading cause of chronic osteomyelitis in patients with sickle cell disease.[53] The first decade of life was reported as the peak age for incidence of chronic osteomyelitis.[54] Osteonecrosis also constituted anatomic dysfunctions in sickle cell disease with multifactorial etiology.[55] Factors associated with increased predisposition to osteonecrosis of the femoral head are euglobulin clot lysis time, hemoglobin level, and co-existence of other variants of abnormal hemoglobin like alpha-thalassemia with hemoglobin SS genotype.[122] Iwegbu and Fleming (1985) revealed the most susceptible age for avascular necrosis, as between 6 and 15 years, and they also indicated that females were more prone to avascular necrosis, compared to males.[56]

Musculoskeletal complications of sickle cell disease have also been explored in the extant literature. Onyemaechi et al and Balogun et al studied the spectrum of musculoskeletal disorders in sickle cell disease.[1,57] They revealed musculoskeletal complications as major root causes of morbidity and disability in people affected with the disease. They also highlighted bacterial infections of bones and joints as a precipitating factor for osteomyelitis and septic arthritis.

Discussion

Interesting findings have emerged from this critical review based on the methodological approach adopted. Majority of the studies were undertaken in the South-Western part of Nigeria, and this was followed by the South-East zone. North-East had the least proportion of articles, and this may be attributed to the current unrest caused by insurgency which has been ongoing for over a decade in the region.[123,124] The ongoing issues relating to the terrorism and insecurity in the North-East may have constituted access and implementation challenges for scientists interested in working in that part of the country. This consequently would reduce research output.

Findings from this review revealed that data utilized for majority of the studies were collected via laboratory tests. Only one out of the reviewed studies adopted a qualitative approach through the use of interviews. This suggests that knowledge gaps may exist, especially in areas where interpretivist epistemologies are best suited to improve practice.[125] Qualitative data collection can encourage communication on critical issues which may be difficult to express in quantitative form. Interpersonal interview has been found to increase confidence as well as clinical outcomes for patients.[49] It is, therefore, critical for more qualitative research be considered in undertaking studies that aim at better understanding sickle cell disease, with a view to improving its management.

A considerable proportion of the studies focused on hematological and serological screening, and this could be due to the fact that sickle cell disease is primarily a blood disorder.[31,58] Similarly, significant problems associated with white blood cells, platelets, and coagulation in sickle cell anemia condition could be responsible for the extensive research in this area.[30,59] Another factor that could have contributed to the preponderance of research in this area could be the routine serologic evaluations of sickle cell patients' body electrolytes, liver enzymes, as well as micro and macro nutrients.[4,34,60–62,90]

Sickle cell disease poses a serious burden to Nigeria's health system and the society at large.[63] In this study, various pathophysiologic effects associated with this condition were identified. Findings revealed relatively lower arterial blood

pressure in patients with sickle cell anemia.[13,18] Furthermore, indicators such as hematocrit, frequency of crisis, body mass index, and body surface area emerged as significant determinants of blood pressure issues for people affected with the disease.[16,64] Additionally, peripheral vascular resistance was identified as a determinant of blood pressure in patients with severe anemia.[14,16]

Findings from this study suggest the presence of electrocardiographic abnormalities among patients with sickle cell disease.[19,20] Electrocardiographic abnormalities observed among these individuals were attributed largely to chronic anemia and vaso-occlusion.[18] Chronic anemia was believed to be responsible for increased cardiac output with a minimal increase in heart rate.[14] Progressive vasculopathy occurring as a result of inflammatory cytokines and oxidative stress was reported to be associated with sickling and intravascular hemolysis, and this also contributed to progressive cardiac lesions with subsequent abnormal electrocardiographic readings.[16]

There were indications from this review that sickle cell disease had significant effect on pregnancy, as severe complications were reported among pregnant women which were accompanied by increased fetal and maternal mortality.[27] Importantly, pain crisis, urinary tract infection, low birth weight, retained placenta and pre-eclampsia were identified as some of the common complications during pregnancy.[26] It is interesting to note that prophylactic transfusion had been shown to reduce the frequency of painful crises in pregnant women.[25]

Morbidity and mortality patterns in hospitalized patients with sickle cell disease indicated vaso-occlusive crisis, abdominal pain, hyper-hemolytic crisis, and acute splenic sequestration, as common clinical presentations. Other parameters identified, include septicemia, acute osteomyelitis, pneumonia, priapism, urinary tract infection, and septic arthritis.[23,59,126] These findings imply the need for development of a contextual framework that emphasises early diagnosis, intensive counseling, and appropriate antibiotic prophylaxis for affected individuals.[65,127]

Evidence from this study also suggests a high level of sexual dysfunction among male patients with sickle cell disease. Priapism was identified as a common sexual organ dysfunction seen among male patients with sickle cell disease between 18 and 20 years of age.[62,66] Risk factors predisposing patients to priapism were unclear,[66] suggesting the need for further research in this area.

This study further revealed a musculoskeletal crisis in sickle cell disease, acute osteomyelitis was seen in children with sickle cell disease, and the tibia bone had been identified as the most common site.[127] This may also be one of the contributing factors to low life expectancy in children with sickle cell disease. Furthermore, leg ulcer was observed to be common among persons suffering from sickle cell anemia.[67,68] Ulceration was believed to occur due to thrombi formation in small capillaries, which consequently results to ischemia. This phenomenon is further promoted by up-regulation of integrins by micro-thrombin which promotes platelets aggregation and adherence to the endothelium.[4,60] Also, the release of injurious cytokines, as well as conditions such as thrombocytosis and antithrombin deficiency, were identified as other factors that may promote ulceration.[69]

Therapeutic red blood cell transfusion remains a cardinal intervention in the management of sickle cell disease. However, blood transfusion could also introduce immune alloantibodies in transfused individuals, with resultant clinical consequences such as hemolytic transfusion reactions and incompatibility crisis.[47] The prevalence of alloantibodies in transfused patients with sickle cell disease is high in Nigeria.[46,121] Likewise, a high prevalence of transfusion transmissible infections had been reported.[40–44] This high prevalence can be attributed to poor screening modalities for blood and blood products in some healthcare facilities. Proper screening of blood before transfusion is therefore critical in reducing this occurrence. Additionally, awareness and educational interventions that improve knowledge regarding voluntary blood donation and screening for blood transmissible infections need to be encouraged.[42,45]

Findings from this study revealed some psychosocial impacts of sickle cell disease.[70] Societal attitudes and perceptions were identified as triggers for major psychosocial issues among sickle cell disease patients. Impaired psychosocial health-related quality of life had been associated with a number of negative effects, including low self-esteem; anxiety and depression; a loss of interest in basic life activities.[71,72] The need for active involvement of social workers in the overarching healthcare for persons with sickle cell disease cannot therefore be over emphasized. Government, non-governmental organizations, and other stakeholders involved in sickle cell care must also synergize efforts in improving psychosocial and socioeconomic support for individuals with sickle cell disease. This is especially fundamental in improving access to health and quality of life for persons with sickle cell disease.[73,74] Several of the clinical issues

observed in this review can be invaluable in contributing to the revision of the 2014 national guideline for the control and management of sickle cell disease.[128]

Current interventions for sickle cell disease in Nigeria were reported to be suboptimal, and this was mainly attributed to a lack of relevant infrastructure and equipment in this area.[129,130] In order to reduce the burden of sickle cell disease in Nigerian setting, there is a need to improve quality of care alongside intensifying relevant campaigns for prevention of the disease.[131,132]

Limitation and Strength

The possible limitation of this review is associated with the search strategy that was limited to the title, keywords and abstract of each article. More in-depth search could have perhaps resulted in identification of more studies. Despite this potential weakness, the review adopted a robust method of analysis through the use of a combination of both descriptive statistical analysis and narrative analysis in the synthesis of various outcomes, and presentation of relevant findings. Further research to determine relevant interventions to cushion the relevant impacts identified in this review can be invaluable in reducing the burden of sickle cell disease in Nigeria.

Conclusion

This study adopted a novel approach to critically review issues relating to sickle cell disease and its health impact on affected individuals in Nigeria. Majority of the articles in this review were undertaken in the South-Western part of the Country, and a considerable proportion of them involved laboratory investigations. Findings from the study revealed that sickle cell disease had both health and social consequences. The disease was identified as a major healthcare issue in Nigeria, given that the country had highest prevalence of sickle cell disease globally, while also contributing to significantly high mortality rates of children under 5 years of age. Key aspects of disease reduction and elimination strategies for sickle cell disorder in Nigeria include continuous enlightenment programmes; social awareness campaigns; and premarital genetic counselling about the condition.

It is also critical to establish more sickle cell clinics with adequate state of the art equipment and well-trained personnel for prompt diagnosis and treatment of various clinical manifestations of sickle cell disease. Further health system-wide measures that can help control and eliminate the disease include free routine genetic screening as well as psychosocial and financial support for persons with sickle cell disease. It is important for sickle cell patients to have access to critical services like stroke risk screening with transcranial doppler ultrasound and pulmonary hypertension risk with echocardiography. Also, it is important to prioritise access to relevant affordable therapies such as hydroxyurea, niprisan, prophylactic antibiotics, antimalarials and other medications. A synergistic implementation of these interventions identified in the study will not only help reduce sickle cell morbidity and mortality for Nigerians with sickle cell disease, they would also make a significant contribution towards controlling and elimination of the disease. The innovative study design adopted by the study enabled the identification of thematic areas, geopolitical zones, methodological approaches and disease specifics neglected by the extant literature. Further robust research in these critical areas can yield strong contextual evidence that will underpin comprehensive strategies for sustainable and impactful policy and practice reforms.

Disclosure

The authors report no conflicts of interest in this work.

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