Nutritional perspectives on sickle cell disease in Africa: A systematic review

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Abstract

Background: Sickle cell disease (SCD), an inherited blood disorder, predominantly affects individuals in sub-Saharan Africa. Research linking its pathophysiology and nutritional status in African patients has not been previously described. This systematic review aimed to assess the landscape of studies in sub-Saharan Africa focused on nutritional aspects of SCD and highlight gaps in knowledge that could inform priority-setting for future research.

Methods: The study was conducted using the Preferred Reporting items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. All original studies involving individuals with any phenotypic variant of SCD and at least one nutritional status outcome, and were conducted between January 1995 and November 2020 in Africa were included. 'Nutritional status' was defined by studies on dietary intake, measurements of growth/anthropometry, or nutritional biomarkers. Studies were included if they involved Databases used were Ovid Embase, Medline, Biosis and Web of Science.

Results: The search returned 526 articles with 76 studies included in the final analyses. Most investigations (67%) were conducted in Nigeria. Studies were categorized into one of three main categories: descriptive studies of anthropometric characteristics (49%), descriptive studies of macro- or micronutrient intakes (41%), and interventional studies (11%). Findings consistently found growth impairment, especially among children and adolescents from sub-Saharan Africa. Studies assessing macro- and micronutrients generally had small sample sizes and were exploratory in nature. Only four randomized trials were identified, which measured the impact of lime juice, long-chain fatty acids supplementation, ready-to-use supplementary food, and oral arginine on health outcomes.

Conclusions: The findings reveal a moderate number of descriptive studies, most with small sample sizes, that focused on various aspects of nutrition and SCD in African patients. There was a stark lack of interventional studies that could be used to inform evidence-based changes in clinical practice. Findings of investigations were generally consistent with data from other regional settings, describing a significant risk of growth faltering and malnutrition among individuals with SCD. There is an unmet need for clinical research to better understand the potential benefits of nutritional-related interventions for patients with SCD in sub-Saharan Africa in order to promote optimal growth and improve health outcomes.

Background

Sickle cell disease (SCD) is the most common inherited blood disease worldwide, with the vast majority of cases occurring in sub-Saharan Africa [1]. The condition derives from a point mutation of the β-globin gene found on the short arm of chromosome 11 through which the hydrophilic amino acid glutamic acid is substituted with the hydrophobic amino acid valine at the sixth position [2,3]. The result is a change in the structure and dynamics of hemoglobin such that certain conditions including deoxygenation and acidosis predispose to hemoglobin polymerization. When this occurs, erythrocytes assume a misshapen and rigid form that promotes pathological processes leading to intravascular inflammation and occlusion of small blood vessels [4]. Since these processes can take place anywhere in the body, the disease is highly complex and characterized by multiple potential life-threatening complications that include acute splenic sequestration, aplastic crises, acute chest syndrome, infection, heart failure, and stroke [5,6]. The disease's clinical hallmarks include acute painful crises and severe anemia [1]. In sub-Saharan Africa, it has been estimated that up to 90% of children born with SCD die before five years of age [7].

In high resource countries, mortality from SCD has decreased dramatically over the past five decades. The improvements in outcomes have been attributed in part to newborn screening and comprehensive care programs designed to prevent disease complications to the extent possible and to treat complications of disease when they occur [8]. Early detection of disease enables clinicians and families to institute measures to proactively prevent complications and facilitate timely treatment when needed. For example, the risk of fatal infection has been shown to be reduced through vaccination and administration of prophylactic antibiotics [9]. Furthermore, treatments with blood transfusion and hydroxyurea therapy has led to superior outcomes in the long term [10,11]. Unfortunately, the availability of vaccines, medicines, and other interventions is highly variable in sub-Saharan Africa. Increasing access to proven preventative and treatment modalities is therefore an urgent priority [12]. At the same time, there is a need to identify new ways of maximizing the well-being of individuals with SCD in Africa and it is in this context that nutritional interventions could possibly play an important role.

There is evidence that the pathophysiology of SCD has substantial nutritional implications including higher energy and nutrients requirements, nutrient deficiencies, and growth abnormalities [13–15]. It is theorized that a main driver of disease complications is higher rates of metabolic expenditure in individuals with SCD resulting from increased hematopoiesis, increased cardiac output, chronic inflammation, and related processes [16,17]. Since nutritional interventions could be a mechanism for addressing increased energy expenditure, attention to nutritional care is increasingly seen to be an important aspect of supportive management for patients with SCD[18,19], especially in resource poor settings. However, evidence-based nutritional guidelines for patients with SCD in Africa are lacking and the extent of nutrition-focused research involving individuals in Africa with SCD is unclear. We undertook this systematic review to evaluate the existing literature focused on nutritional aspects of SCD in sub-Saharan Africa. Specifically, we sought to assess the number and nature of relevant studies, review their findings, and identify gaps in knowledge that could inform priority-setting for future research.

Methods

Eligibility criteria. We sought to include all studies involving original research that focused on the nutritional status of individuals with SCD in an African population. Studies involving nutritional status were defined as those that investigated topics of dietary intake, measurements of growth or anthropometry,
or nutrition-related biomarkers. Studies that did not differentiate the cause of the anemia were excluded, as were studies that only included nutrition interventions as part of a comprehensive care program. Studies involving both children and adults were included. The focus of this analysis was on studies involving individuals with various forms of SCD including HbSS, HbSC, and rarer genetic variants of disease; studies were excluded that only involved individuals with sickle cell trait. Case reports and review articles were also excluded.

**Informational sources and search strategy.** The databases employed for this search were Ovid Embase, Medline, Biosis, and Web of Science. The date range was January 1st, 1995, through November 30th, 2020, such that the reference list covered a period of approximately 25 years. We performed a Boolean search using specific Boolean operators and the following search terms: “Sickle cell disease” or “sickle cell anemia” or “hemoglobinopathy” AND Africa or specific African countries (all African countries were individually listed) AND various nutrition-related terms (i.e., nutrition, growth, macronutrient, micronutrient, vitamin, mineral, anthropometric, height, length, weight, head circumference, mid-upper arm circumference, MUAC, dietary intake, recommended dietary allowance, RDA, nutritional status) along with associated terms (both indexed and non-indexed) for nutrition, diet and growth, and specific vitamins and minerals. We also allowed for inclusion of articles that were identified through review of the bibliographies of papers that underwent full-text review. Investigations written in any language were included provided sufficient translation into English could be assured.

**Data management and selection process.** Titles and abstracts were each screened by two independent reviewers. Any title or abstract that appeared to meet inclusion criteria or for which there was uncertainty prompted a full text review. Reviewing of full text articles were assigned to individual investigators. If eligibility of a full text article was unclear, it was resolved by discussing it with at least two other reviewers on the research team who were not earlier assigned the full text article using the inclusion criteria. To maximize consistency among reviewers, each reviewer initially reviewed 10 articles and the review team together discussed the initial dataset that had been extracted to ensure accuracy and completeness. The review process then proceeded according to the process described.

**Data synthesis.** Study data were extracted into standardized forms using Microsoft Excel (Microsoft, Redmond, USA) where it was organized for analyses. Depending on the nature of the articles that met inclusion criteria, we extracted information relating to geography, subject age group, sample size, comparison groups, biomarkers, and other relevant variables. Since the main purpose of this investigation was to broadly understand the types of nutrition-related studies that have been conducted involving individuals with SCD in Africa, we chose not to systematically judge the quality of evidence or risks of bias within individual studies. Rather, we discussed specific merits and limitations of individual studies where appropriate in the context of major themes that would emerge in the analyses. We planned for a quantitative categorization of the types of articles (e.g., descriptive versus interventional studies) and a narrative synthesis of data in table and text format to summarize and assess the results.

**PRISMA.** The study was conducted and reported according to PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines [20,21].

**Results**

**Search results.** In total, 526 unique titles and abstracts were identified through the literature search. Of those, 347 did not meet inclusion criteria and 179 full-text articles were assessed. Seventy-six studies were deemed eligible and included in the final analyses (Figure 1).

**Results overview.** The majority of investigations (67%) were conducted in a single country (Nigeria). Each study was placed into one of three main categories according to the primary nature of the investigation: (a) descriptive study of anthropometric characteristics (37 articles; 49%); (b) descriptive study of macro- or micronutrient intake or status (31 articles; 41%); and (c) interventional studies (8 articles; 11%). The studies are summarized in Tables 1-3 and described in greater detail below.

**Descriptive studies of anthropometric characteristics.** Nearly one-half of all studies identified focused on anthropometric characteristics. The studies typically assessed height, weight, and body mass index (BMI). Other measurements included head circumference, arm span, and various body composition parameters.

The majority (25/37; 68%) of studies were conducted in Nigeria. Other studies involved populations in Democratic Republic of Congo (DRC) [22–24], Ghana [25,26], Tanzania [27], Egypt [28], Cameroon [29], and Algeria [30]. In addition, two multi-country studies involved patients in Cameroon, Ivory Coast, Gabon, Mali, and Senegal [31,32]. The majority of reports focused on children and adolescents; only one study exclusively involved adults [33]. Most studies evaluated approximately 50-200 patients and a similar number of age- and gender-matched healthy controls; three large studies enrolled over 1,000 SCD patients each [27,31,32]. Several studies used WHO growth standards for comparison rather than a non-sickle cell disease control group. Male and female subjects were generally equally represented in the study populations.
The three largest studies found significant growth defects compared to healthy controls. A multi-country study of more than 3,500 SCD patients (aged 10-24 years) with nearly 1,000 controls in Cameroon, Ivory Coast, Gabon, Mali, and Senegal was designed to evaluate determinants of vascular complications. Anthropometric analyses showed that SCD patients were significantly shorter and had lower BMI than controls; weight was not reported. A caveat of the study was that the control group was significantly older (median age 24 vs 16 for patients) and more likely to be female (60% vs 54% for patients) than the SCD group. A follow-up study involving the same subject population revealed significantly higher rates of growth failure, defined as a height and/or weight and/or BMI below the 5th percentile using WHO growth reference [32]. Another large study followed a cohort of approximately 1,000 SCD patients aged 6 months to 48 years over 5 years and found SCD to be significantly associated with stunting, underweight, and wasting, with the most pronounced effects associated with adolescent age and male gender [27]. Adult men were seven times more likely than adult women to be underweight and were significantly more likely to be stunted and wasted. Females demonstrated improved catch-up growth compared with males following growth deficits that were identified during adolescence.

The studies involving smaller sample sizes showed greater variation in the results, but some trends emerged. Several reports confirmed the finding that males were more likely to show growth deficits than females [34–37]. Multiple studies also noted that growth deficits became more pronounced with age. For example, a study that involved young patients aged 6-35 months showed no association with wasting, stunting, or underweight status [38]. A study of 233 children aged 2-17 years with SCD in Lagos, Nigeria found that the factor most significantly associated with both wasting and stunting was older age. Additional studies similarly detected one or more growth deficits in adolescents but not in younger children [39–44]. In several Nigerian studies, SCD patients were found to be underweight or to have low BMI, but showed no difference in height compared to controls [37,42,45–48]. Other studies showed differences in both weight and height [33,35,36,47,49,50]. These variable findings may have resulted from the fact that the studies were not powered to detect significant differences in height specifically. Reports from DRC, Egypt, and Ghana found that children with SCD had a higher prevalence of stunting compared to controls, but did not always show differences in wasting or BMI [23,25,28]. SCD was also associated with delayed puberty [28,51].

Three studies from Nigeria reported the presence of overweight and obesity among patients with SCD although in lower proportions (an average of less than 3% of the sample population) [34,46,52].

**Descriptive studies of macronutrient or micronutrient levels.** The second most common group of studies identified involved assessment of biomarkers from serum samples for macronutrients or micronutrients. Most studies were conducted in Nigeria (21/31, 68%); other studies took place in DRC [53], Tanzania [27,54,55], Egypt [56], Kenya [38], Ghana [57], Uganda [58], and Malawi [59]. Nutritional parameters measured included proteins/amino acids, fatty acids, vitamins, and minerals. The majority of studies included less than 100 individuals with SCD. Both children and adults were studied, with male and female subjects generally equally represented.

Serum protein levels were investigated in one small study (13 children with SCD and 17 healthy controls) in Nigeria in which no significant differences were reported in the concentrations of total protein or albumin between SCD patients and controls [37]. However, serum prealbumin levels were significantly lower for the population of patients with SCD, which was hypothesized to result from poor nutrition or existing disease-related inflammation. The serum concentrations of all amino acids except alanine, glutamic acid, and proline were significantly reduced in SCD patients. A small study involving 23 participants in Tanzania measured the steady state nutrition status of SCD patients who later died (n=11) compared with those who were alive at the end of the study period. Those who suffered mortality had a significantly lower BMI, plasma taurine levels and arginine bioavailability before succumbing [60].

Proportions of fatty acid and the state of metabolism were evaluated in four related studies of young SCD patients in Nigeria [35,49,61,62]. These reports found perturbed pathways of fatty acid elongation and desaturation in children with SCD. Specifically, arachidonic acid, eicosapentanoic acid (EPA), and docosahexanoic acid (DHA) were significantly reduced, whereas saturated (palmitic acid) and monounsaturated (oleic acid) were significantly elevated in patients compared to controls. Another study in a population of 26 SCD patients aged 11-43 in Enugu, Nigeria, confirmed the finding that EPA and DHA fatty acids are reduced in SCD patients [63]. The authors of these studies hypothesized that reduced polyunsaturated fatty acids in the phospholipids of the cell membrane of SCD patients could lead to their being more rigid, thereby contributing to disease symptoms. A study of 30 children with SCD in Egypt found that patients also had significantly lower cholesterol, triglycerides, and LDL (but not HDL) in blood plasma compared to healthy controls [56].

Acknowledging that interpretation of plasma concentrations of vitamins and minerals can be problematic in patients with ongoing inflammation, analysis of serum vitamin levels in SCD patients generally indicated lower concentrations of vitamin A [63,64] vitamin C [64,65] and vitamin E [56,59,63,64]. One study of 14 SCD patients in Kenya found no association of HbSS phenotype and low concentrations vitamin A [38]. Three reports of a related study in children with SCD patients [66–68] When compared to healthy controls, mean 25-hydroxyvitamin D levels were significantly lower in SCD patients and suboptimal vitamin D levels were seen in greater than 10% of patients. However, no SCD patients with severe vitamin D deficiency (defined as <20 ng/ml) were observed. A limitation of the latter two studies was the lack of a healthy comparator group; each used vitamin D deficiency cut-off values for a healthy population in other published studies as reference.
Selected minerals were evaluated in eight small studies of SCD patients and compared to healthy controls. Serum iron concentration was reduced in patients compared to controls in all studies that evaluated it [57,69–71]. Serum or plasma zinc was also generally reduced in SCD patients [53, 70–74], although zinc was elevated in one population of 59 Nigerian adult SCD patients [69]. Measures of other minerals showed mixed results. Magnesium levels were either reduced [71,72], elevated [73] or unchanged [69,71,75] in SCD patients compared to healthy controls. Similarly, copper was reduced [72], elevated [57,73,76] or unchanged [69,71] in SCD patients. Other minerals measured in only a few studies included manganese, chromium, selenium, potassium, rubidium, cadmium, and calcium.

**Interventional studies.** A very small number of clinical studies involving nutritional interventions in SCD patients in African countries were identified. There were four randomized trials [77–80]. The first was a study of 125 SCD patients in Nigeria (involving children aged 1 year and above) that tested the effect of lime juice on SCD parameters. All patients in the treatment group (n=65) as well as controls (n=60) were given folic acid, vitamin B complex, and proguanil, with the treatment group also given twice-daily oral lime juice with weight-based dosing ranging from 5-15 mL. Each child was assessed monthly for 6 months. The group receiving lime juice was reported to have significantly fewer pain episodes, febrile illnesses, and hospital admission rates. There was no change in transfusion rate, organomegaly, or jaundice. The positive effect was postulated to result from vitamin C, amino acids (in particular, phenylalanine), and flavonoids contained in the juice, but no direct evidence for this was provided [77].

A second study of 128 SCD patients aged 2-24 years in Sudan investigated the impact of one year of treatment with oral omega-3 capsules containing EPA and DHA fatty acids (using age- and weight-dependent dosing) compared to placebo. The hypothesis was that omega-3 fatty acids could reduce red blood cell aggregation, adherence, and inflammation that occur during sickle cell disease-mediated vaso-occlusive crises. The treatment group had significantly fewer clinical vaso-occlusive events, as well as reduced rates of severe anemia and need for blood transfusions. The study was not powered to detect changes in other outcomes such as stroke, sequestration crisis, or vascular necrosis [78].

A third trial utilized a double-blind, random order design. Ready-to-use-supplementary food was studied in 119 children with SCD in Tanzania [79]. Two different formulations of the supplements were compared: a commercially available (Nutriset, France) ready-to-use-supplementary food (RUSF) fortified with vitamins and minerals according to recommended daily allowances and an "enhanced" version of the same RUSF that was additionally fortified with arginine and citrulline. Arginine is the substrate for endothelial nitric oxide synthase, a natural vasodilator, and has been implicated in pathophysiology of SCD complications. In the cross-over study design, children received each treatment for 4 months, with 4-month washout periods following the intervention. Ready-to-use-supplementary food led to small weight gains, an increased arginine bioavailability ratio, and improved measures of endothelial function compared to baseline; addition of arginine and citrulline to the supplement did not provide additional benefits [79].

The final randomized study identified involved the regular administration of oral arginine therapy to 35 hospitalized patients with SCD in Nigeria and compared the effects with 33 control subjects. Plasma arginine levels increased by 125% in the arginine arm compared with 29% in the control arm [80]. Arginine treatment was associated with quicker discharge and reduced pain events. The rate of adverse events was non-significant between the two treatment arms, however there was a trend towards increased vomiting in the patients treated with arginine. A previous study outside of Africa also found positive clinical effects associated with the use of arginine [81].

One of the non-randomized interventional studies identified investigated the use of vitamin D supplementation. A small treatment arm was nested in a Nigerian study comparing blood levels of vitamin D and pro-inflammatory cytokines [68]. The hypothesis was that low vitamin D levels might lead to a pro-inflammatory environment that exacerbates SCD symptoms. Twelve children with SCD who were determined to have low vitamin D levels were given 3 months of oral vitamin D supplementation (2000 U). At the end of treatment, mean serum 25-hydroxyvitamin D levels were significantly increased compared to baseline, levels of several proinflammatory cytokines were significantly decreased, and the levels of anti-inflammatory cytokine IL-11 were significantly increased.

**Discussion**

To our knowledge this is the first review of nutrition-related studies involving individuals living with SCD in sub-Saharan Africa. While a moderate number of studies were identified, most were descriptive in nature and small in terms of numbers of subjects. Approximately two-thirds of studies took place in a single country (Nigeria). In addition, there were very few interventional trials designed to measure the impact of an isolated nutritional intervention and only four randomized studies. The findings of this review suggest an outstanding need for nutrition-focused research relating to the care of individuals with SCD in Africa, with a particular emphasis on research with practical implications for clinical management in order to improve patient outcomes.
The findings of studies identified through this review are generally consistent with nutrition-related investigations involving SCD patients in other parts of the world. More than fifty years ago, poor growth was first reported in patients with SCD, and that observation has since been repeated in multiple studies involving SCD populations in Jamaica, Brazil, India, and North America [13,15,82–88]. Many of these studies specifically note that the growth faltering occurred in patients that were receiving recommended daily protein and calorie intakes. The pathophysiology of growth problems in SCD patients has come into sharper focus in recent decades. A leading view is that the increased rate of red cell turnover, a primary feature of SCD patients, underlies a hypermetabolic state. The biochemical and physiological factors that contribute to hypermetabolism include increased protein turnover, increased myocardial activity, and production of proinflammatory cytokines [89–93]. The supposition is that the energy and nutrient requirements normally recommended are not adequate in patients with SCD given their increased energy expenditures and other unusual metabolic demands, which compete directly with energy needs required to sustain adequate growth.

Evidence derived from robust interventional studies is important to support recommendations for specific nutrition-related practices for patients with sickle cell disease. Only four randomized trials were identified. The studies were small, each involving less than 150 individuals with SCD. Positive clinical benefits were found with the use of lime juice, long-chained fatty acid supplementation, RUSF, and oral arginine; ideally these findings would be confirmed in larger follow-up investigations. It is worth noting the paucity of robust interventional trials designed to test the effect of macronutrient supplementation in individuals with SCD despite the evidence, as described above, that nutrition deficits in this population are likely to be caused at least in part from the increased energy demands that result from altered metabolism.

Guidelines for clinical management of patients with SCD published by internationally recognized organizations do not provide special guidance for nutritional care [94,95]. Given that the risk of poor growth in SCD patients is increasingly reported, and the fact that there is plausible pathophysiologic drivers of nutritional disturbances in SCD patients, there appears to be a substantial gap in research in this area to inform much needed evidence-based recommendations.

Limitations of this systematic review include the fact that nearly half of studies identified were largely anthropometry-based descriptive studies. Few studies involving nutritional interventions in sub-Saharan Africa were identified, only several had robust methodologies, and none have been validated in repeated studies. In addition, the studies involving analyses of vitamin and mineral levels in SCD patients in sub-Saharan Africa overall involved small numbers of patients and generally were unable to link findings with meaningful clinical correlations in ways that might influence nutritional care practices. Another limitation is that most investigations identified took place in the single country of Nigeria (at the same time, acknowledging that Nigeria is home to the largest population of SCD patients globally).

Conclusion

Despite the reality that most SCD patients globally live in sub-Saharan Africa, and the fact that nutritional disturbances in SCD patients are increasingly well described, there has been limited research focused on ways that nutritional care might help to improve clinical outcomes in this patient population. A systematic review of the literature revealed studies that consistently reported stunted growth and malnutrition in African SCD patients during childhood and adolescence, but failed to identify robust, validated studies that could be used to inform clinical management. Our study suggests an outstanding need to determine if and how supportive nutritional care can reduce disease severity and improve health outcomes for individuals with SCD in sub-Saharan Africa. As such, priority research in this area in the future may include systematic assessment of the drivers of nutritional status in SCD patients, studies that directly advance the understanding of macro- and micronutrient deficiencies associated with clinically significant physiologic effects, and investigations that evaluate the impact of nutritional interventions in order to inform evidence-based nutritional guidance.

List Of Abbreviations

SCD - Sickle Cell Disease
EPA - Eicosapentanoic Acid
DHA - Decosahexanoic Acid
PRISMA- Preferred Reporting items for Systematic Reviews and Meta-Analysis

Declarations

Ethics approval and consent to participate

Not applicable
Consent for publication

Not applicable

Availability of data and materials

All data generated or analysed during this study are included in this published article

Competing Interests

Rajiv Shah is an employee of the Novartis Global Health and Corporate Responsibility. Jonathan Spector is an employee at Novartis Institutes for BioMedical Research.

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Author's contributions

EBN was responsible for coordinating the entire project and is the guarantor of the review. EBN, CJ, JS, and MSA developed the project. EBN, CJ, RS, AKD and JS reviewed the abstracts and articles included in this study and carried out the data collection. EBN, CJ, JS, and MSA participated in the analyses. EBN and CJ wrote the first version of the manuscript. AJ, AKD, EM, AO, RS, JS, SAA, ABB, HIH and MSA reviewed and edited the manuscript during its production. All authors read and approved the final manuscript.

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References

1. Ware RE, de Montalembert M, Tshilolo L, Abboud MR. Sickle cell disease. Lancet. 2017;390: 311–323. doi:10.1016/S0140-6736(17)30193-9
2. Pauling L, Itano H. Sickle cell anemia a molecular disease. Science (80- ). 1949;110: 543–8.
3. Ingram VM. Abnormal human haemoglobins. I. The comparison of normal human and sickle-cell haemoglobins by fingerprinting. Biochim Biophys Acta. 1958;28: 539–45. doi:10.1016/0006-3002(58)90516-x
4. Bunn H, Forget B. Hemoglobin: Molecular, genetic and clinical aspects. Philadelphia, PA, USA: WB Saunders; 1986.
5. Mbanya N. Sickle cell disease in subsaharan Africa. Vox Sang. 2015;109: 63–64.
6. Otoikhian CSO, Okoror LE. Sickle cell disease african killer. Biologists alternative. Int J Pharma Med Biol Sci. 2012;1: 232–245.
7. Grosse SD, Odame I, Atrash HK, Amendah DD, Piel FB, Williams TN. Sickle cell disease in Africa: A neglected cause of early childhood mortality. Am J Prev Med. 2011;41: S398-405. doi:10.1016/j.amepre.2011.09.013
8. Consensus conference. Newborn screening for sickle cell disease and other hemoglobinopathies. JAMA. 1987;258: 1205–9. Available: http://www.ncbi.nlm.nih.gov/pubmed/3626004
9. Lanzkron S, Carroll CP, Haywood C. Mortality Rates and Age at Death from Sickle Cell Disease: U.S., 1979–2005. Public Health Rep. 2013;128: 110–116. doi:10.1177/003335491312800206
10. Tshilolo L, Tomlinson G, Williams TN, Santos B, Olupot-Olupot P, Lane A, et al. Hydroxyurea for Children with Sickle Cell Anemia in Sub-Saharan Africa. N Engl J Med. 2019;380: 121–131. doi:10.1056/NEJMoa1813598
11. Adams RJ, McKie VC, Hsu L, Files B, Vichinsky E, Pegelow C, et al. Prevention of a first stroke by transfusions in children with sickle cell anemia and abnormal results on transcranial Doppler ultrasonography. N Engl J Med. 1998;339: 5–11. doi:10.1056/NEJM199807023390102
12. McGann PT. Time to Invest in Sickle Cell Anemia as a Global Health Priority. Pediatrics. 2016;137: e20160348–e20160348. doi:10.1542/peds.2016-0348
13. Al-Saqladi A-WM, Cipolotti R, Fijnvandraat K, Brabin B. Growth and nutritional status of children with homozygous sickle cell disease. Ann Trop Paediatr. 2008;28: 165–189. doi:10.11179/146532808X335624
14. Bello-Manga H, DeBaun MR, Kassim AA. Epidemiology and treatment of relative anemia in children with sickle cell disease in sub-Saharan Africa. Expert Rev Hematol. 2016;10:101–1042. doi:10.1080/174474086.2016.1240612

15. Platt OS, Rosenstock W, Espeland MA. Influence of Sickle Hemoglobinopathies on Growth and Development. N Engl J Med. 1984;311: 7–12. doi:10.1056/NEJM198407053110102

16. Akohoue SA, Shankar S, Milne GL, Morrow J, Chen KY, Ajayi WU, et al. Energy expenditure, inflammation, and oxidative stress in steady-state adolescents with sickle cell anemia. Pediatr Res. 2007;61: 233–8. doi:10.1203/pdr.0b13e31802d7754

17. Hyacinth Hl, Gee BE, Hibbert JM. The Role of Nutrition in Sickle Cell Disease. Nutr Metab Insights. 2010;3: 57–67. doi:10.4137/nmi.s5048

18. Canadian Haemoglobinopathy Association. Consensus Statement on the Care of Patients with Sickle Cell Disease in Canada. Ottawa; 2014.

19. National Health Service. Sickle Cell Disease in Childhood: Standards and Guidelines for Clinical Care. 2010.

20. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ. 2009;339: b2700. Available: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2714672&tool=pmcentrez&rendertype=abstract

21. Shamseer L, Moher D, Clarke M, Gherisi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (prisma-p) 2015: Elaboration and explanation. BMJ. 2015;349. doi:10.1136/bmj.g7647

22. Mikobi TM, Lukusa Tshilobo P, Aloni MN, Akilimali PZ, Mvumbi-Lelo G, Mbuyi-Muamba JM. Clinical phenotypes and the biological parameters of Congolese patients suffering from sickle cell anemia: A first report from Central Africa. J Clin Lab Anal. 2017;1. doi:10.1002/jcla.22140

23. Lukusa Kazadi A, Ngiyulu RM, Gini-Ehungu JL, Mbuyi-Muamba JM, Aloni MN. Factors Associated with Growth Retardation in Children Suffering from Sickle Cell Anemia: First Report from Central Africa. Africa. 2017;1. doi:10.1155/2017/7916348

24. Arigliani M, Kitenge R, Castriott L, Ndjule P, Barbato V, Cogo P, et al. Lung function in children with sickle cell disease from Central Africa. Thorax. 2019;74: 604–606. doi:10.1136/thoraxjnl-2018-212720

25. Osei-Yeboah C, Rodrigues Q, Enweronu-Laryea C. Nutritional status of children with sickle cell disease at Korle Bu Teaching Hospital, Accra, Ghana. West Afr J Med. 2011;30: 262–267.

26. Osei TB, Apprey C, Mills-Robertson FC, Ohemeng AN. Nutritional status of children with sickle cell disease: A study at the Komfo Anokye Teaching Hospital of Ghana. Nutr Food Sci. 2019;49: 232–239. doi:10.1108/NFS-03-2018-0100

27. Cox SE, Makani J, Fulford AJ, Komba AN, Soka D, Williams TN, et al. Nutritional status, hospitalization and mortality among patients with sickle cell anemia in Tanzania. Haematologica. 2011;96: 948–953. doi:10.3324/haematol.2010.028167

28. Soliman AT, ElZalabany M, Amer M, Ansari BM. Growth and pubertal development in transfusion-dependent children and adolescents with thalassaemia major and sickle cell disease: A comparative study. J Trop Pediatr. 1999;45: 23–30. doi:10.1093/jtroped/45.1.23

29. Um SSN, Seungue J, Alima AY, Mbono R, Mbassi H, Chelo D, et al. A cross sectional study of growth of children with sickle cell disease, aged 2 to 5 years in Yaoundé, Cameroon. Pan Afr Med J. 2019;34. doi:10.11604/pamj.2019.34.85.16432

30. Tebbani F, Rouabah L, Grifi F, Boudiba N, Rouabah A, Necib Y. Descriptive approach for sickle cell disease in Eastern of Algeria. Int J Pharm Sci Res. 2014;25: 97–101.

31. Ranque B, Menet A, Boutouyrie P, Diop IB, Kingue S, Diarra M, et al. Arterial stiffness impairment in sickle cell disease associated with chronic vascular complications. Circulation. 2016;134: 923–933. doi:10.1161/CIRCULATIONAHA.115.021015

32. Alexandre-Heymann L, Dubert M, Diallo DA, Diop S, Tolo A, Belinga S, et al. Prevalence and correlates of growth failure in young African patients with sickle cell disease. Br J Haematol. 2019;184. doi:10.1111/bjh.15638

33. Aderibigbe A, Omotoso AB, Awobusuyi JO, Akande TM. Arterial blood pressure in adult Nigerian sickle cell anaemia patients. West Afr J Med. 1999;18: 114–118.

34. Esezobor CI, Akintan P, Akinsulie A, Temiye E, Adeyemo T. Wasting and stunting are still prevalent in children with sickle cell anaemia in Lagos, Nigeria. Ital J Pediatr. 2016;42. doi:10.1186/s13052-016-0257-4

35. Glew RH, Casados J, Huang YS, Chuang LT, VanderJagt DJ. Correlation of the fatty acid composition and fluid property of the cholesteryl esters in the serum of Nigerian children with sickle cell disease and healthy controls. Prostaglandins Leukot Essent Fat Acids. 2003;68: 61–68. doi:10.1016/S0952-3278(02)00275-2

36. VanderJagt DJ, Bonnett C, Okolo SN, Glew RH. Assessment of the bone status of Nigerian children and adolescents with sickle cell disease using calcaneal ultrasound and serum markers of bone metabolism. Calcif Tissue Int. 2002;71: 133–140. doi:10.1007/s00223-001-1107-x

37. VanderJagt DJ, Kanellis GJ, Isichei C, Pastuszyn A, Glew RH. Serum and urinary amino acid levels in sickle cell disease. J Trop Pediatr. 1997;43: 220–225. doi:10.1093/tropej/43.4.220

38. Tsang BL, Sullivan KM, Ruth L, Williams TN, Suchdev PS. Nutritional status of young children with inherited blood disorders in Western Kenya. Am J Trop Med Hyg. 2014;90: 955–962. doi:10.4269/ajtmh.13-0496

39. Oredugba F, Savage K. Anthropometric finding in Nigerian children with sickle cell disease. Pediatr Dent. 2002;24: 321–325.

40. Senbanjo IO, Oshikoya KA, Salisu M, Diaku-Akinwumi IN. Head circumference of children with sickle cell disease in Lagos, Nigeria. Pan Afr Med J. 2016;25. doi:10.11604/pamj.2016.25.8.8030

41. Akodu SO, Diaku-Akinwumi IN, Kehinde OA, Njokanma OF. Evaluation of Arm Span and Sitting Height as Proxy for Height in Children with Sickle Cell Anemia in Lagos, Nigeria. J Am Coll Nutr. 2014;33: 437–441. doi:10.1080/07315724.2013.875356
69. Olaniyi JA, Arinola OG. Nitric oxide and trace metals in relation to haemoglobin F concentration in Nigerian sickle cell disease patients. Turkish J Med Sci. 2010;40: 109–113. doi:10.3906/sag-0901-30

70. Ojo JO, Oluwole AF, Osoniyo RO, Durosinimi MA, Aboderin AO. Determination of trace elements status of Nigerians with sickle cell anaemia using INAA and PIXE. Afr J Med Med Sci. 2006;35: 461–467.

71. Arinola OG, Olaniyi JA, Akiibinu MO. Evaluation of antioxidant levels and trace element status in Nigerian sickle cell disease patients with Plasmodium parasitae. Pakistan J Nutr. 2008;7: 766–769. doi:10.3923/pjn.2008.766.769

72. Ajayi G. Zinc, magnesium, and copper concentrations in serum, erythrocytes, and urine in sickle cell homozygotes and heterozygote Nigerian women. Trace Elem Electrocytes. 1997;14: 69–71.

73. Akenami FO, Aken'Ova YA, Osifo BO. Serum zinc, copper and magnesium in sickle cell disease at Ibadan, south western Nigeria. Afr J Med Med Sci. 1999;28: 137–139.

74. Kudrat AA, Shehu UA, Kolade E, Ibrahim M. Serum zinc level during and after acute painful episodes in children with sickle cell anemia at the amin kano teaching hospital, Kano, Northern Nigeria. Niger J Clin Pract. 2019;22: 16–23. doi:10.4103/njcp.njcp_169_18

75. Olaldeo OQ, Temiye EO, Ezeaka VC, Obomanu P. Serum magnesium, phosphate and calcium in Nigerian children with sickle cell disease. West Afr J Med. 2005;24: 120–123. doi:10.4314/wajm.v24i2.28180

76. Emokpae MA, Fatimehin EB, Obazelu PA. Serum levels of copper, zinc and disease severity scores in sickle cell disease patients in Benin City, Nigeria. Afr Health Sci. 2019;19: 2798–2805. doi:10.4134/ahs.v19i3.56

77. Adegoke SA, Shehu UA, Mohammed LO, Sanusi Y, Oyelami OA. Influence of Lime Juice on the Severity of Sickle Cell Anemia. J Altern Complement Med. 2013;19: 588–592. doi:10.1089/acm.2012.0567

78. Daak AA, Ghebremeskel K, Hassan Z, Attallah B, Azan HH, Elbashir MI, et al. Effect of omega-3 (n-3) fatty acid supplementation in patients with sickle cell anemia: Randomized, double-blind, placebo-controlled trial. Am J Clin Nutr. 2013;97: 37–44. doi:10.3945/ajcn.112.036319

79. Cox SE, Ellins EA, Marealle AI, Newton CR, Soka D, Sasi P, et al. Ready-to-use food supplement, with or without arginine and citrulline, with daily chloroquine in Tanzanian children with sickle-cell disease: a double-blind, random order crossover trial. Lancet Haematol. 2018;5: E147–E160. doi:10.1016/S2352-3026(18)30020-6

80. Onalo R, Cooper P, Cilliers A, Nnebe-Agumadu U, Oniyangi O, Oladimeji D, et al. Oral arginine therapy as a novel adjuvant in the management of acute pain in children with sickle cell anemia in Nigeria: A randomized placebo-controlled trial. Blood. 2019;134: 613. doi:10.1182/blood-2019-122510

81. Morris CR, Kyupers FA, Lavrisha L, Ansari M, Sweeters N, Stewert M, et al. A randomized, placebo-controlled trial of arginine therapy for the treatment of children with sickle cell disease hospitalized with vaso-occlusive pain episodes. Haematologica. 2013;98: 1375–82. doi:10.3324/haematol.2013.086637

82. Scott R, Ferguson A, Jenkins M, Clark H. Studies in sickle-cell anemia. VIII. Further observations on the clinical manifestations of sickle cell anemia in children. AMA Am J Dis Child. 1955;90: 682–91. Available: http://www.ncbi.nlm.nih.gov/pubmed/13268049

83. Whitten C. Growth Status of Children with Sickle-Cell Anemia. Arch Pediatr Adolesc Med. 1961;102: 355. doi:10.1001/archpedi.1961.02080010357009

84. Heyman MB, Vichinsky E, Katz R, Gaffield B, Hurst D, Castillo R, et al. Growth retardation in sickle-cell disease treated by nutritional support. Lancet. 1985;1: 903–6. doi:10.1016/s0140-6736(85)91677-0

85. Ashcroft MT, Serjeant GR, Desai P, Heights, weights, and skeletal age of jamaican adolescents with sickle cell Anaemia. Archives of Disease in Childhood. 1972. doi:10.1136/adc.47.254.519

86. Nikhar H, Shinde G, Meshram S. An anthropometric and hematological comparison of sickle cell disease children from rural and urban areas. Indian J Hum Genet. 2012;18: 40. doi:10.4103/0971-6866.96643

87. Mitchell MJ, Carpenter GJO, Crosby LE, Bishop CT, Hines J, Noll J. Growth status in children and adolescents with sickle cell disease. Pediatr Hematol Oncol. 2009. doi:10.1080/08880010902896882

88. Silva CM, Viana MB. Growth deficits in children with sickle cell disease. Arch Med Res. 2002. doi:10.1016/S0188-4409(01)00360-5

89. Badaloo A, Jackson AA, Jahoor F. Whole body protein turnover and resting metabolite rate in homozygous sickle cell disease. Clin Sci. 1989;77: 93–7. doi:10.1042/cs0770093

90. Hibbert JM, Gaspari MS, Gaffield B, Hurst D, Castillo R, et al. Erythropoiesis and myocardial energy requirements contribute to the hypermetabolism of childhood sickle cell anemia. J Pediatr Gastroenterol Nutr. 2006;43: 680–7. doi:10.1097/01.mgp.0000228120.44606.d6

91. Hibbert JM, Hsu LL, Bhathena SJ, Irune I, Sarbo B, Creaey MS, et al. Proinflammatory Cytokines and the Hypermetabolism of Children with Sickle Cell Disease. Exp Biol Med. 2005;230: 68–74. doi:10.1177/153537020523000109

92. Umeakunne K, Hibbert JM. Nutrition in sickle cell disease: recent insights. Nutr Diet Suppl. 2019;11: 9–17. doi:10.2147/nds.s168257

93. Yawn BP, Buchanan GR, Afenyi-Annan AN, Ballas SK, Hassell KL, James AH, et al. Management of sickle cell disease: Summary of the 2014 evidence-based report by expert panel members. J Am Med Assoc. 2014;312: 1033–1048. doi:10.1001/jama.2014.10517

94. National Institutes of Health. Evidence-based management of sickle cell disease. Expert Panel Report, 2014.

95. Vanderjagt DJ, Trujillo MR, Jalo I, Bode-Thomas F, Glew RH, Agaba P. Pulmonary function correlates with body composition in Nigerian children and young adults with sickle cell disease. J Trop Pediatr. 2008;54: 87–93. doi:10.1093/tropej/fmm070
97. Akingbola TS, Tayo BO, Salako B, Layden JE, Hsu LL, Cooper RS, et al. Comparison of patients from Nigeria and the USA highlights modifiable risk factors for sickle cell anemia complications. Hemoglobin. 2014;38: 236–243. doi:10.3109/03630269.2014.927363

98. Oluwole OB, Noll RB, Winger DG, Akinyanju O, Novelli EM. Cognitive functioning in children from Nigeria with sickle cell anemia. Pediatr Blood Cancer. 2016;63: 1990–1997. doi:10.1002/pbc.26126

99. Arigliani M, Castriotta L, Zubair R, Dogara LG, Zuiani C, Raywood E, et al. Differences in lung function between children with sickle cell anaemia from West Africa and Europe. Thorax. 2019;74: 1154–1160. doi:10.1136/thoraxjnl-2019-213717

100. Ukoha OM, Emodi IJ, Ikefuna AN, Obidike EO, Izuka MO, Eke CB. Comparative study of nutritional status of children and adolescents with sickle cell anemia in Enugu, Southeast Nigeria. Niger J Clin Pract. 2020;23: 1079–86. doi:10.4103/njcp.njcp_476_19

101. Anyanwu JN, Williams O, Sautter CL, Kasiye P, Hume H, Opoka RO, et al. Novel Use of Hydroxyurea in an African Region With Malaria: Protocol for a Randomized Controlled Clinical Trial. JMIR Res Protoc. 2016;5: e110. doi:10.2196/resprot.5599

102. Ajibola KA, Adedokun KA, Oduola T, Oparinde DP, Ayelagbe OG, Ojokuku HO. Assessment of iron status and interplay between lipid peroxidation and antioxidant capacity in common hemoglobin variants in Osun State, southwestern Nigeria. Kaohsiung J Med Sci. 2019;35. doi:10.1002/kjm2.12062

103. Erhabor O, Ogar K, Erhabor T, Dangana A. Some haematological parameters, copper and selenium level among children of African descent with sickle cell disease in Specialist Hospital Sokoto, Nigeria. Hum Antibodies. 2019;27: 143–154. doi:10.3233/HAB-180360

104. Afolabi IS, Osikoya IO, Fajimi OD, Osoro PI, Ogunleye DO, Bisi-Adeniyi T, et al. Solenostemon monostachyus, Ipomoea involucrata and Carica papaya seed oil versus Glutathione, or Vernonia amygdalina: Methanolic extracts of novel plants for the management of sickle cell anemia disease. BMC Complement Altern Med. 2012;12: 262. doi:10.1186/1472-6882-12-262

105. Imaga NA, Chukwu CE, Blankson A, Gbenle GO. Biochemical assessment of Ciklavit®, a nutraceutical used in sickle cell anemia management. J Herb Med. 2013;3: 137–148. doi:10.1016/j.hermed.2013.05.003

106. Kaddam L, Fadl-Elmula I, Eisawi OA, Abdelrazig HA, Saeed AM. Acacia Senegal (gum Arabic) supplementation modulate lipid profile and ameliorated dyslipidemia among sickle cell anemia patients. J Lipids. 2019. doi:10.1155/2019/3129461

Tables

Table 1. Studies of anthropometric characteristics of individuals living with sickle cell disease in Africa
| Authors and year of publication | Location | Ages | No. of subjects | Control group | Weight | Height | Body mass index | Other assessments |
|-------------------------------|----------|------|----------------|--------------|--------|--------|-----------------|-------------------|
| VanderJagt et al., 1997[37]   | Jos, Nigeria | 10 months-14 years (mean 7 years for males; mean 6 years for females) | 13 | 17 age- and gender-matched controls | Significantly lower weight in males with SCD | No significant differences in height reported | No statistical difference in BMI as both weight and height were lower for SCD patients | · Significantly lower head circumference in males with SCD versus controls  
· No differences in MUAC or triceps skin fold  
· No differences reported for females |
| Soliman et al., 1999[28]     | Alexandria, Egypt | Mean 7 years | 110 | 200 healthy age-matched children, 30 children with constitutional growth delay, 25 children with growth hormone deficiency | N/A | · Height and growth velocity significantly lower in SCD patients than healthy controls  
· Bone age delay in SCD patients by 2.4 years | BMI not significantly different between SCD patients and healthy controls | · Lower MUAC and triceps skin fold thickness in SCD patients versus healthy controls  
· Significant age delays in puberty in SCD patients |
| Aderibigbe et al., 1999[33]  | Ilorin, Nigeria | 18-54 years (mean 22 years) | 64 | 60 adults aged 18-57 | Significantly lower weight in individuals with SCD | Significantly shorter height in individuals with SCD | N/A |
| VanderJagt et al., 2000[42]  | Jos, Nigeria | 3-20 years | 48 | 51 healthy controls | Significantly lower weight in males with SCD aged 10-18 years; no differences for females | Significantly lower height in females and males with SCD | Significantly lower BMI for males with SCD aged 10-18; no differences for females | · Significantly lower fat free mass in males with SCD aged 10-18  
· Significantly higher body fat and % body fat in individuals with SCD aged ≥10 years |
| Vandegt et al., 2002[49]    | Jos, Nigeria | Mean 13 years for males and females | 72 | 68 age- and gender-matched controls | Significantly lower weight in females and males with SCD | Significantly lower height in females and males with SCD | Significantly lower BMI in females and males with SCD | · Significantly lower bone density in individuals with SCD by ultrasound measurement  
· Some differences in serum markers of bone resorption and formation  
· No differences in triceps skin fold  
· Significantly lower MUAC, FFM, and % FFM in males and females with SCD; males with SCD also had |
| Study & Year       | Location       | Age Range          | Sample Size | Findings                                                                 | Notes                                                                 |
|-------------------|----------------|--------------------|-------------|--------------------------------------------------------------------------|----------------------------------------------------------------------|
| Oredugba et al., 2002[39] | Lagos, Nigeria | 1-18 years (mean 10 years) | 117         | Significantly lower weight in individuals with SCD aged 18 years          | No differences in MUAC in individuals with SCD                        |
|                   |                |                    |             |                                                                           | No differences in mean head circumference                             |
| Glew et al., 2003[35]  | Jos, Nigeria   | 10-18 years (mean 14 years for males; mean 13 years for females) | 77          | Significantly lower weight in individuals with SCD                        | Significantly lower height in individuals with SCD; no differences for females |
|                   |                |                    |             |                                                                           |                                                                      |
| VanderJagt et al., 2007[96] | Jos, Nigeria   | 7-35 years (mean 15 years for males; mean 17 years for females) | 102         | Significantly lower weight in individuals with SCD                        | Significantly lower BMI in males with SCD; no differences for females |
|                   |                |                    |             |                                                                           |                                                                      |
| Aina et al., 2010[51] | Lagos, Nigeria | 10-19 years (mean 14 years) | 136         | N/A                                                                      | N/A                                                                  |
|                   |                |                    |             |                                                                           |                                                                      |
| Cox et al., 2011[27]  | Dar es Salaam, Tanzania | 6 months-48 years (mean 10 years) | 1041        | SCD status was significantly associated with underweight; adult males were more likely to be underweight than females | SCD was significantly associated with stunting; adult males were more likely to be stunted than females |
|                   |                |                    |             |                                                                           | SCD was significantly associated with wasting; adult males were more likely to have wasting than females |
| Osei-Yeboah, 2011[25] | Ghana          | 1-12 years (mean 7 years) | 357         | Significantly lower weight-for-age in individuals with SCD                | Prevalence of stunting higher in individuals with SCD (35%) versus controls (3%) |
|                   |                |                    |             |                                                                           |                                                                      |

Legend:
- **Significantly lower body fat**
- **Significantly lower weight in individuals with SCD**
- **Significantly lower height in individuals with SCD**
- **Significantly lower BMI in males with SCD; no differences for females**
- **Significantly lower FFM in individuals with SCD; no differences in FFM% and fat %**
- **Significantly lower phase angle (measure of overall nutritional status) in individuals with SCD**
- **Significantly lower MUAC and triceps skin fold in females with SCD (not for males)**
- **Prevalence of malnutrition higher in individuals with SCD (61%) versus controls (29%)**
- **No significant differences in rates of wasting**
| Study                          | Location          | Age Group | Sample Size | Comparison                                                                                   | Findings                                                                                           |
|-------------------------------|-------------------|-----------|-------------|--------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|
| Iwalokun et al., 2011 [43]    | Lagos, Nigeria    | 5-35 years| 55 (31 steady-state and 24 unstable/crisis) | 22 “non-SCD” individuals                                                                 | Significantly lower weight for males >16 years; not different in other age groups                  |
|                               |                   |           |             |                                                                                            | N/A                                                                                               |
|                               |                   |           |             |                                                                                            | Significantly lower BMI in females with SCD (all age groups) and males with SCD (>16 years)       |
|                               |                   |           |             |                                                                                            | · Significantly lower fat mass in males with SCD (>16 years); not significantly different for other age groups |
|                               |                   |           |             |                                                                                            | · Significantly lower leptin levels in males with SCD (≤16 years) and all female age groups        |
| Animasahun et al., 2011 [45]  | Lagos, Nigeria    | 1-10 years (mean 6 years) | 100          | 100 individuals with phenotype HbAA matched by age, socio-economic class, and gender           | Significantly lower mean weight and weight-for-height in individuals with SCD                      |
|                               |                   |           |             |                                                                                            | Mean height showed no difference between SCD patients and controls                                 |
|                               |                   |           |             |                                                                                            | No difference in mean BMI                                                                             |
| Akodu et al., 2012 [52]       | Lagos, Nigeria    | 2-15 years (mean 8 years) | 80           | 80 individuals with phenotype HbAA                                                             | No statistical difference reported                                                                |
|                               |                   |           |             |                                                                                            | N/A                                                                                               |
|                               |                   |           |             |                                                                                            | Significantly lower BMI in individuals with SCD                                                    |
| Tebbani et al., 2014 [30]     | Annaba city, Algeria | 6-12 years | 30           | WHO standard references                                                                        | Lower weight in individuals with SCD compared with WHO standards                                 |
|                               |                   |           |             |                                                                                            | Height was below WHO standard references for SCD patients                                          |
|                               |                   |           |             |                                                                                            | N/A                                                                                               |
| Akingbola et al., 2014 [97]   | Ibadan, Oyo, Nigeria and Chicago, USA | 11-30 years | 214          | 209 individuals with SCD aged 11-30 years living in USA (compares characteristics of individuals with SCD in Nigeria to those in US) | Significantly lower weight in individuals with SCD in Nigeria vs US in patients ≥18 years old    |
|                               |                   |           |             |                                                                                            | Significantly lower height in individuals with SCD in Nigeria vs US in patients ≥18 years old      |
|                               |                   |           |             |                                                                                            | Significantly lower BMI in individuals with SCD in Nigeria vs US in patients ≥18 years old        |
| Akodu et al., 2014 [41]       | Lagos, Nigeria    | 8 months-15 years (mean 6 years) | 100          | 100 HbAA age- and sex-matched controls                                                        | Significantly lower sitting height in individuals with SCD aged >10 years; height not significantly different |
|                               |                   |           |             |                                                                                            | N/A                                                                                               |
|                               |                   |           |             |                                                                                            | N/A                                                                                               |
|                               |                   |           |             |                                                                                            | Significantly shorter arm span in individuals with SCD aged >10 years                               |
| Tsang et al., 2014 [38]       | Nyanza Province, Western Kenya | 6-35 months | 14           | 288 children from random sample of 882; Underweight, stunting and wasting were defined using WHO 2006 standards | No significant association of HbSS with underweight                                              |
|                               |                   |           |             |                                                                                            | No significant association of HbSS with stunting                                                   |
|                               |                   |           |             |                                                                                            | No significant association of HbSS with wasting                                                     |
| Eke et al., 2015 [44]         | Enugu, Nigeria    | 6-18 years (mean 11 years) | 132          | 132 age- and gender-matched HbAA children and adolescents from nearby schools                  | Significantly lower weight in females with SCD aged 10-18 years; no differences in males          |
|                               |                   |           |             |                                                                                            | No differences in height-for-age                                                                  |
|                               |                   |           |             |                                                                                            | N/A                                                                                               |
|                               |                   |           |             |                                                                                            | · No differences in body fat % or visceral fat %                                                    |
|                               |                   |           |             |                                                                                            | · Significantly lower skeletal muscle % in males with SCD aged 6-9 years                           |
| Eke et al., 2015 [46]         | Enugu, Nigeria    | 1-5 years (mean 3 years) | 58           | 58 age- and gender-matched HbAA individuals                                                   | Significantly lower weight-for-age in individuals with SCD                                        |
|                               |                   |           |             |                                                                                            | No difference in height-for-age                                                                  |
|                               |                   |           |             |                                                                                            | N/A                                                                                               |
|                               |                   |           |             |                                                                                            | · Significantly lower BMI in individuals with SCD                                                   |
|                               |                   |           |             |                                                                                            | · Significantly lower weight-for-height in individuals with SCD                                    |
| Study Reference         | Country/Region                  | Age Range | Sample Size | Weight | Height | BMI | Factors (P<0.01) |
|-------------------------|---------------------------------|-----------|-------------|--------|--------|-----|-----------------|
| Ranque et al., 2016[31]| Cameroon, Ivory Coast, Gabon, Mali, Senegal | 10-24 years (median 16 years) | 3,627 | N/A | Significantly lower height in individuals with SCD (3.4% vs 22.4%) |
| Odetunde et al., 2016[47]| Enugu State, Nigeria          | 6-20 years (mean 12 years) | 40 | Significantly lower weight in individuals with SCD | N/A | 48% with SCD were overweight (BMI < 5th percentile); 13% of controls were underweight |
| Esezobor et al., 2016[34]| Lagos, Nigeria                | 2-17 years (mean 9 years) | 233 | Compared with WHO 2007 standards | 23% of individuals with SCD had wasting (low weight-for-height) or severe wasting | No differences in height | 12% of SCD patients were stunted or severely stunted; 75.5% were normal height |
| Senbanjo et al., 2016[40]| Lagos, Nigeria                | Children up to age 15 years (mean 7 years) | 118 (114 HbSS and 4 HbSC phenotype) | Significantly higher rate of "thinning" in individuals with SCD aged 11-15 years | Significantly higher rate of stunting in individuals with SCD aged 11-15 years | N/A | No overall difference in mean head circumference |
| Oluwole et al., 2016[98]| Lagos, Nigeria                | 6-16 years (mean 9 years) | 56 | Significantly lower weight-for-age in individuals with SCD | Significantly lower height in individuals with SCD | N/A |
| Adegoke et al., 2017[68]| Ilesa, Nigeria                | 4-11 years | 95 | Significantly lower BMI in individuals with SCD | Significantly lower BMI in individuals with SCD | N/A | Significantly lower BMI in patients with greater disease severity |
| Mikobi et al., 2017[22]| Kinshasa, Democratic Republic of Congo | Mean 25 years | 140 | Study compared groups of SCD patients stratified by disease severity | N/A | N/A |
| Kazadi et al., 2017[23]| Kinshasa, Democratic Republic of Congo | Under 12 years | 159 | Significantly lower weight in individuals with SCD (39.6% of individuals with SCD versus 12.2% of controls) | Significantly more stunting in individuals with SCD (34.6% in individuals with SCD versus 9.8% of controls) | N/A | Factors significantly associated (P<0.01) with poor growth included frequency of crises, age <1 yr. at first |
were defined using WHO 2006 standards

| Study                                      | Location                  | Age (years) | Sample Size | Gender | Height, Weight, BMI | Significance |
|-------------------------------------------|---------------------------|-------------|-------------|--------|---------------------|--------------|
| Sokunbi et al., 2017[50]                  | Nigeria                   | 5-18        | 175         |        | No statistical difference reported | Significantly lower height in individuals with SCD |
| Onukwuli et al., 2018[48]                 | Enugu, Nigeria            | 6-18        | 81          | females only | 81 age- and socio-economic class-matched HbAA individuals | No differences in mean height |
| Osei et al., 2019[26]                     | Kumasi, Ghana             | 3-12        | 100         |        | Compared with WHO growth standards | 37% of individuals with were underweight |
| Sap Ngo Um et al., 2019[29]               | Yaoundé, Cameroon         | 2-5         | 77          |        | Compared with WHO growth standards | 4% of subjects were underweight and 5% of subjects were wasted |
| Alexandre-Heymann et al., 2019[32]       | Cameroon, Ivory Coast, Gabon, Mali, Senegal | 5-21        | 2583; phenotypes included SS, Sβ0, SC, Sβ+ |        | 287 HbAA or HbAS individuals | See "other assessments" |
| Arigliani et al., 2019[99]               | Kaduna, Nigeria           | 6-18        | 154         |        | 364 age-matched controls | Significantly increased rate of wasting in individuals with SCD |
| Arigliani et al., 2019[24]               | Kinshasa, Democratic Republic of Congo | 6-18        | 112         |        | 377 schoolchildren controls | Significantly increased rate of wasting in individuals with SCD |
| Ukoha et al., 2020[100]                   | Enugu, Nigeria            | 1-18        | 175         |        | 175 age-, gender-, and socioeconomic status-matched HbAA individuals | Significantly lower Z-score for height-for-age in individuals with SCD; and significantly higher rate of wasting in individuals with SCD (using WHO) |
Table 2. Studies of macronutrient or micronutrient levels in individuals living with sickle cell disease in Africa
| Authors and year of publication | Location          | Ages                                      | No. of subjects | Control group                                      | Nutrient type | Findings                                                                 |
|---------------------------------|-------------------|-------------------------------------------|-----------------|---------------------------------------------------|---------------|--------------------------------------------------------------------------|
| VanderJagt et al., 1997[37]     | Jos, Nigeria      | 10 months – 14 years                      | 13              | 17 age- and gender-matched controls               | Proteins/amino acids | - No significant differences in concentrations of total protein, albumin, serum creatinine, or albumin/globulin ratios  
- Significantly reduced serum prealbumin levels in individuals with SCD  
- Significantly reduced serum concentrations of all essential amino acids and most non-essential amino acids (exceptions: alanine, glutamic acid, proline) in individuals with SCD |
| Cox et al., 2011[60]            | Dar-es-Salaam, Tanzania | Mean 17-18 years                          | 11 patients who had succumbed | 12 age- and gender-matched controls (all patients had SCD; comparison was between those alive and those who had succumbed) | Proteins/amino acids | - Significantly lower BMI, a trend for lower taurine levels, and significantly lower l arginine bioavailability in individuals with SCD who later succumbed  
- No differences in hemolytic markers (unconjugated bilirubin, lactate dehydrogenase, aspartate transaminase, alkaline phosphate), with the exception that conjugated bilirubin at enrollment was significantly higher in patients who later succumbed compared to those who did not |
| Enomoto et al., 1998[61]        | Jos, Nigeria      | Females mean 6.3 years; males mean 6.8 years | 13              | 14 age-matched controls                           | Fatty acids    | - No difference in proportions of linoleic and α-linolenic fatty acids  
- Significantly increased levels of palmitic acid and oleic acid in individuals with SCD  
- Significantly reduced levels of arachidonic acid, eicosapentanoic acid, and docosahexaenoic acid |
| Glew et al., 2002[62]           | Jos, Nigeria      | 5-17 years (mean 13 years)                | 77              | 73 age- and gender-matched controls               | Fatty acids    | - No differences in levels of linoleic acid  
- Significantly reduced α-linolenic acid and arachidonic acid in females with SCD; no difference in males  
- Significantly reduced eicosapentanoic acid and docosahexaenoic acid in individuals with SCD  
- Significantly increased proportions of palmitic acid (16:0) and oleic acid (18:1n-9) in serum phospholipids in individuals with SCD |
| VanderJagt et al., 2002[49]     | Jos, Nigeria      | Females mean 13.2 years; males mean 13.4 years | 72              | 68 age- and gender-matched controls               | Fatty acids    | - No differences in linoleic and α-linolenic acid  
- Significantly reduced long chain polyunsaturated fatty acids and arachidonic acid in individuals with SCD  
- Significantly higher palmitic acid and oleic acid in individuals with SCD |
| Glew et al., 2003[35]           | Jos, Nigeria      | 9-20 years (mean 14 years for males; mean 13 years for females) | 77              | 75 age- and gender-matched healthy controls       | Fatty acids    | - Significantly reduced linoleic acid, arachidonic acid, α-linolenic acid, eicosapentanoic acid, and docosahexaenoic acid in serum cholesterol esters in individuals with SCD  
- Significantly increased palmitic acid and oleic acid in serum cholesterol esters in individuals with SCD |
| Hamdy et al., 2015[56]          | Cairo, Egypt      | 6-18 years (mean 12 years)                | 30              | 30 age- and gender-matched controls               | Fatty acids and vitamins | - Significantly reduced cholesterol, triglycerides, and LDL in individuals with SCD  
- No differences in HDL |
| Ren et al., 2008[63] | Enugu, Nigeria | 11–43 years | 26 | 30 HbAA individuals aged 22–53 years | Fatty acids and vitamins | Significantly reduced levels of selenium and vitamin E in individuals with SCD |
|---------------------|----------------|------------|-----|-----------------------------------|------------------------|---------------------------------------------|
|                     |                |            |     |                                   |                        | Significantly reduced eicosapentaenoic acid and docosahexaenoic acid in red blood cell choline phosphoglycerides in individuals with SCD |
|                     |                |            |     |                                   |                        | Significantly reduced plasma retinol, α-tocopherol, and β-carotene concentrations, and reduced activity of red cell copper/zinc-superoxide dismutase, in individuals with SCD |
| Shukla et al., 1999[59] | Malawi | 2-19 years (mean 9 years) | 28 | 20 HbAA individuals aged 22–53 years | Vitamins | Reduced vitamin E levels in 12 children (63%) |
|                     |                |            |     |                                   |                        | Reduced vitamin E/cholesterol ratio in 10 children (36%), indicating vitamin E deficiency |
| Jiya et al., 2005[64] | Sokoto, Nigeria | 9 months – 12 years (mean 6 years) | 27 | 38 HbSS individuals and 11 with HbSS and persistent fetal hemoglobin | Vitamins | Significantly lower vitamin A (retinol), vitamin C (ascorbic acid) and vitamin E (α-tocopherol) in individuals with SCD |
| Cox et al., 2011[65] | Tanzania | 2-15 years (median 8 years) | 23 | 18 siblings aged 2-12 years (median 7 years) | Vitamins | Vitamin C deficiency identified in 48% of individuals with SCD |
| Tsang et al., 2014[38] | Nyanza Province, Western Kenya | 6-35 months | 14 | 288 individuals from a random sample of 882 | Vitamins | No significant association with vitamin A deficiency |
| Adegoke et al., 2017[67] | Ile-Ife, Nigeria | Mean age 7 years | 95 | 75 age- and gender-matched HbAA individuals | Vitamins | Significantly reduced mean serum 25-hydroxy vitamin D in individuals with SCD |
| Adegoke et al., 2017[68] | Ilesa, Nigeria | 4-11 years (mean 7 years) | 95 | 109 Brazilian children with SCD aged 4-11 years (study compares SCD populations in Nigeria and Brazil) | Vitamins | Suboptimal vitamin D levels in 12.6% of Nigerian individuals with SCD; none had severe vitamin D deficiency |
| Adegoke et al., 2017[66] | Nigeria | 1-15 years (mean 8 years) | 123 | Study examined effect of vitamin D levels on pain (no control group) | Vitamins | Deficient or insufficient serum 25-hydroxyvitamin D (vitamin D) in 11% of individuals with SCD; none had severe vitamin D deficiency |
| Siegert et al., 2018[58] | Uganda | 1-4 years | 99 | Individuals with SCD randomly selected from the NOHARM study[101] | Compared with standard reference values | Vitamins | 53% of children were vitamin D-insufficient (unrelated to inflammation) |
| Ajayi et al., 1997[72] | Lagos, Nigeria | Mean 21 years | 30 (females only: 10 HbSS, 10 HbAS, 10 HbAC) | 10 HbAA individuals | Minerals | Significantly reduced zinc levels in individuals with SCD compared to heterozygotes and HbAA controls |
|                     |                |            |     |                                   |                        | Significantly reduced mean serum and erythrocyte copper in individuals with SCD compared to heterozygotes and HbAA controls |
|                     |                |            |     |                                   |                        | Significantly reduced serum, erythrocyte, and urine magnesium in individuals with SCD compared to heterozygotes and HbAA controls |
| Akenani et al., 1999[73] | Ibadan, Nigeria | 16-42 years | 35 (23 HbSS, 12 HbSC) | 25 age- and gender-matched HbAA individuals | Minerais | Significantly reduced serum zinc in individuals with HbSS and HbSC |
|                     |                |            |     |                                   |                        | Significantly increased serum copper and magnesium in individuals with HbSS; no difference in individuals with HbSC |
| Study                  | Location            | Age/Time               | Sample Size | Control Details | Minerals                                                                 |
|-----------------------|---------------------|------------------------|-------------|-----------------|---------------------------------------------------------------------------|
| Oladipo et al., 2005  | Lagos, Nigeria      | 7-170 months           | 86          | Min 45 age- and gender-matched HbAA individuals | Minerals:  
  - Significantly increased serum phosphorus in individuals with SCD  
  - Significantly reduced serum calcium in individuals with SCD  
  - No differences in serum magnesium and albumin |
| Ojo et al., 2006      | Ile-Ife, Nigeria    | 10-60 years            | 84 (divided by multiple methods of analysis and sample sites)  | 141 (divided by multiple methods of analysis and sample sites) | Minerals:  
  - Elevated erythrocyte sodium in individuals with SCD  
  - Significantly reduced potassium, zinc, iron, and riboflavin in whole blood and/or erythrocytes in individuals with SCD |
| Arinola et al., 2008  | Ibadan, Nigeria     | Not stated             | 20 individuals with HbSS without malaria; 24 individuals with HbSS with malaria  | 18 HbAA individuals with malaria; 32 HbAA individuals without malaria | Minerals:  
  - Significantly reduced iron, zinc, and magnesium in individuals with SCD compared to controls  
  - Significantly increased urea in non-malaria infected individuals with SCD compared with non-malaria infected controls  
  - Significantly reduced levels of total antioxidants in non-malaria infected individuals with SCD compared with non-malaria infected controls  
  - No differences in magnesium, copper, chromium, cadmium, and selenium in non-malaria infected individuals with and without SCD  
  - No differences in levels of serum albumin |
| Olaniyi et al., 2010  | Ibadan, Nigeria     | 26-55 years            | 59          | 35 age- and gender-matched controls | Minerals:  
  - Significantly increased mean plasma levels of zinc and nitric oxide in individuals with SCD  
  - Significantly reduced levels of serum iron, chromium, and selenium in individuals with SCD  
  - No differences in levels of magnesium, manganese, and copper |
| Cox et al., 2012      | Tanzania            | 3-15 years (mean 8 years) | 32         | No control group | Minerals: Nocturnal hemoglobin oxygen desaturation in individuals with SCD associated with higher transferrin saturation |
| Onukwuli et al., 2017 | Enugu, Nigeria      | 6-18 years             | 81 (females only) | 81 age- and socioeconomic class-matched HbAA individuals from outpatient clinic | Minerals: Significantly reduced levels of serum zinc in individuals with SCD |
| Sangu et al., 2018    | Kasumbalesa, Congo  | 2-15 years (mean 10 years) | 76         | 76 age-, gender-, and residence area-matched controls | Minerals: Significantly reduced levels of zinc and magnesium in individuals with SCD |
| Lee et al., 2018      | Tanzania            | 3-18 years             | 199        | No control group | Minerals: Lower hepcidin in more severely anemic individuals with SCD |
| Ajibola et al., 2019  | Osun State, Nigeria | Median age 24 years    | 60         | 60 individuals with phenotypes SS or SC | Minerals:  
  - Malondialdehyde and superoxide dismutase significantly higher in Hb variants compared to controls  
  - Glutathione and total antioxidant stats levels significantly reduced in Hb variants  
  - Overall results suggested that SCD patients & carriers were more vulnerable to oxidative stress |
| Emokpae et al., 2019  | Benin City, Nigeria | 4-20 years             | 100 HbSS individuals | 50 age- and gender matched HbAA individuals | Minerals: Significantly higher serum copper levels and significantly lower zinc levels in individuals with SCD compared to controls |
| Antwi-Boasiako        | Accra, Ghana        | Mean ages ranged 21-49 | 90 HbSS and HbSC | 50 HbAA individuals | Minerals:  
  - Significantly higher serum iron and copper in individuals with SCD |
Kudirat et al., 2019[74]  
Kano, Nigeria  
6 months-15 years  
140 (70 with acute pain crises, 70 in steady state)  
70 HbAA individuals  
Minerals  
Significantly lower serum zinc level in individuals with SCD compared to controls, which was made worse during vaso-occlusive crises

Erhabor et al., 2019[103]  
Sokoto, Nigeria  
1-15 years  
45  
25 age-matched HbAA individuals  
Minerals  
Significantly lower mean serum copper and selenium in individuals with SCD

| Table 3. Studies of nutritional interventions involving individuals living with sickle cell disease in Africa | 38 years old (depending on phenotype) | individuals | compared to controls |
|---|---|---|---|
| - Serum iron and copper were further increased in patients with HbSS and vaso-occlusive crises |
| - Serum zinc levels were significantly lower in individuals with SCD, especially during vaso-occlusion |
| Authors and year of publication | Location | Ages | No. of subjects | Intervention | Nutrient intervention type | Design | Outcome | Comments |
|---------------------------------|----------|------|-----------------|-------------|---------------------------|--------|---------|----------|
| Afolabi et al., 2012[104]        | Lagos State and Ogun State, Nigeria | 15-48 years | Not reported | Seed oils from *Solenostemon monostachyus*, *Ipomoea involucrate* and *Carica papaya* plants | Plant extract/seed oil | In vitro comparisons using blood from SCD patients; comparison groups were controls, cells treated with glutathione, and cells treated with a known anti-sickling plant extract | · All plant extracts studied led to reduction in sickled red blood cells, reduction in Fe$^{2+}$/Fe$^{3+}$ ratios, and reduction in lactate dehydrogenase activity when compared with controls | Some gender dependent differences were noted; specific bioactive compounds within each plant extract were not isolated |
| Imaga et al., 2013[105]         | Lagos State, Nigeria | 15-28 years | 4 (2 treated, 2 controls) | Oral ingestion for two weeks of a commercial product made from *Cajanus Cajan* plant extract | Plant extract/seed oil | Non-blinded in vitro comparison study | · Treatment group reported to have anti-sickling effect, but no statistical analyses performed | Statistical analyses lacking for main outcomes |
| Kaddam et al., 2019[106]        | Khartoum, Sudan | 5-42 years | 47 | Acacia Senegal (gum Arabic) supplementation as a lipid-lowering agent | Plant extract/seed oil | Single-arm trial | Treatment led to significantly decreased total cholesterol, triglycerides, and low-density lipoprotein; no effect on high-density lipoprotein | Gum Arabic is a dried, gummy substance obtained from the acacia Senegal tree |
| Adegoke et al., 2013[77]        | Ekiti State, Nigeria | 1 year to "adolescent" (upper range not specified) | 125 (65 treated, 60 controls) | Oral ingestion for 6 months of freshly squeezed lime juice; dose was weight-dependent (range: 10-30 ml daily) | Micronutrient | Open label, randomized study | · Treated group had significantly fewer pain episodes, febrile illness, and admission rate | Effect hypothesized to result from vitamin C, amino acids (especially phenylalanine) and flavonoids |
| Adegoke et al., 2017[67]        | Ile-Ife, Nigeria | Mean age 7 years | 170 (95 treated, 75 controls) | Oral ingestion for 3 months of vitamin D supplementation | Micronutrient | Age- and gender-matched controlled study | · Children with SCD and low 25-OHD levels had enhanced levels | Effect hypothesized to result from anti-inflammatory |
in children with SCD that had low 25-hydroxyvitamin D (25-OHD) levels

| Study | Location | Age | Sample Size | Intervention | Study Design | Findings |
|-------|----------|-----|-------------|--------------|--------------|----------|
| Daak et al., 2013[78] | Khartoum, Sudan | 2-24 years | 128 (67 treated, 61 controls) | Oral ingestion for 1 year of Omega-3 capsules containing EPA and DHA fatty acids; dose was weight-dependent | Double-blinded, placebo-controlled, randomized study | - Treatment with vitamin D in children with SCD that had low 25-OHD levels led to an improved pro-inflammatory cytokine profile<br> - Treatment group had improved primary outcome: significantly fewer clinical vaso-occlusive events<br> - Treatment group also had reduced severe anemia, reduced blood transfusions, reduced white blood cell counts, and reduced school absences due to disease<br> - No change in rates of stroke, sequestration crisis, or vascular necrosis |
| Cox et al., 2018[79] | Dar-es-Salaam, Tanzania | 8-12 years (mean 10 years) | 119 | Oral ingestion of ready-to-use supplementary food (RUSF) with and without arginine and citrulline | Double-blind, random order crossover trial | - RUSF increased the global arginine bioavailability ratio and improved measures of endothelial function, and led to improvements in growth<br> - RUSF fortified with arginine and citrulline did not additionally increase the plasma global arginine bioavailability ratio or improve endothelial function<br> - Arginine is the sole substrate of endothelial nitric oxide synthase and has been implicated in pathophysiology of SCD complications |
| Onalo et al., 2019[80] | Abuja, Nigeria | 5-17 years (mean 11 years) | 68 (35 treated, 33 controls) | Oral arginine therapy every 8 hours until discharge in SCD patients hospitalized with severe vaso-occlusive events | Double-blind, randomized, placebo-controlled trial | - Plasma arginine levels increased by 125% (arginine arm) vs 29% (placebo arm)<br> - 54% of children treated with arginine were discharged compared to 24% in placebo arm by day 5<br> - Arginine treatment appeared to ameliorate some measures of pain<br> - Arginine had previously been shown to have benefits in individuals with SCD in studies performed in the United States |
No significant differences in adverse events but arginine arm trended more towards vomiting compared to placebo.