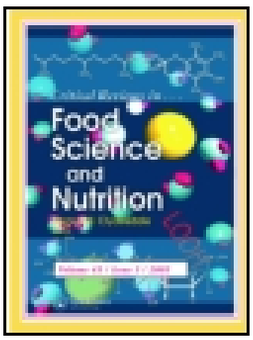

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The role of nutrition in the pathophysiology and management of sickle cell disease among Children: A Review of literature

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Abstract

Sickle cell disease (SCD) is one of the common inherited blood disorders in humans and has been associated with decreased dietary intake which results in poor nutritional status and impaired growth. Nutrition is one of the most important but often forgotten aspect of care of patients with chronic disorders and there have been emerging concern in literature on increased nutritional needs of SCD patients. This paper sought to review the available literature on the roles of individual nutrients in the pathophysiology and management of SCD among children. Children with SCD have been shown to exhibit sub-optimal status with respect to both macro- and micro-nutrients. Thus, nutrition could play an important role in the management of SCD. However, there is paucity of evidence coming from trials with large sample sizes to support the suggestion that supplementation with various nutrients that have been considered in this review will be helpful.

Keywords: sickle cell disease, nutritional management, painful episodes, children

Introduction

Sickle cell disease (SCD) is one of the common inherited blood disorders in humans and has a widespread distribution in different parts of the world with variable clinical manifestations. SCD is a group of genetic disorders that affects haemoglobin synthesis, the molecule in red blood cells that delivers oxygen to cells throughout the body. It is characterized by the predominance of sickle haemoglobin (HbS) produced as a result of a point mutation in the substitution of valine for glutamic acid in the β-globin polypeptide chain (Moheeb *et al.*, 2007). The main consequences resulting from this abnormality are vaso-occlusive events and increased haemolysis. Vaso-occlusive events may lead to bone, tissue, and organ damage while chronic haemolysis may lead to anaemia with base line haemoglobin level as low as 6.0g/dl (Makani *et al.*, 2007; Stuart and Nagel, 2004). SCD patients also have increased susceptibility to infections (Nuzzo & Fonseca, 2004; Booth, Inusa & Obaro, 2010).

Since its discovery, the understanding of the metabolic pathways and pathophysiology of SCD have improved substantially, resulting in the better management and treatment of the disease manifestations among patients. Advances in the clinical care of children with SCD, such as earlier diagnosis, penicillin prophylaxis, folate supplementation, blood transfusion and hydroxyurea therapy have reduced morbidity and mortality (Zemel *et al*., 2007). However, co-morbidities such as pain, stroke, and anorexia which are associated with SCD are likely to lead to decreased dietary intake which in turn results in poor nutritional status, impaired growth, and delayed skeletal and sexual maturation. Impaired growth may among children with SCD may partly be due to nutrient inadequacies, and some studies have shown that nutrient

supplementation of these children led to improvement in growth indices (Zemel *et al*., 2002). Although there are some studies that have reported on nutritional status of children with SCD (Cox *et al.*, 2011; Osei-Yeboah *et al.*, 2011), there is limited information regarding the specific ways in which various nutrients in our diets relate to this health condition among children. There is therefore the need to ascertain the roles of different nutrients and whether nutritional interventions can be incorporated into the care process so as to provide a holistic management tool for SCD. This paper therefore seeks to review the existing literature within the period 1985-2016 on the role of nutrition in the pathophysiology and management of SCD among children.

Sickle cell epidemiology

Sickle cell disease affects almost all populations across the globe. Approximately 300,000 children are born every year with SCD in the world with majority (70%) of the disease occurring in Africa (Ansong *et al.*, 2013; Justus *et al*., 2015). The sickle cell gene also has a wide spread distribution in some parts of Europe, the Americas and the Caribbean (Center for Disease Control and Prevention, 2016). This is mainly due to the Atlantic slave trade as well as the economic migration of Africans to these parts of the world. In Germany and UK for example, there are currently an estimated 1000 and 12,500 patients with SCD respectively (Jaeckel *et al.*, 2010). In the United States, SCD affects approximately 100,000 people and each year, 2000 new diagnoses are detected via newborn screening (Arnold *et al.*, 2015). In India, the beta sickle (βS) gene is prevalent especially in the tribal populations and the prevalence rate varies from 0-40% in different population groups (Mukherjee and Gangakhedkar, 2004). In sub-Saharan African countries such as Cameroon, Republic of Congo, Gabon, Ghana, and Nigeria, the prevalence of

sickle cell trait and SCD has been estimated to be 25% and 2% respectively with Nigeria recording the highest prevalence of SCD in the world (Adegoke and Kuteyi, 2012). In countries where the trait prevalence is above 20% the disease affects about 2% of the population (WHO, 2010). For example in Ghana where the sickle cell trait is 25%, it has been documented that about 2% of neonates are affected by SCD leading to 14,000 new cases annually (Wilson *et al*., 2012). The geographic distribution of the sickle-cell trait is very similar to that of malaria. The sickle cell trait has a partial protective effect against malaria, and this may explain why it has been maintained at such high prevalence levels in Africa (Bartolucci, 2014).

Interaction between nutrition and SCD

Sickle cell patients often report decreased appetite, possibly because of the chronic inflammatory state and inadequate education concerning nutritional requirements which results in several nutritional deficiencies and poor clinical outcomes (Figure 1). These nutrient deficiencies are associated with immunologic, growth, and maturation abnormalities (Hyacinth *et al*., 2013). Although nutrient deficiencies that occur among SCD patients are poorly understood, several factors have been proposed for the limited energy and nutrients observed among these patients. These include; reduced intake potentially from the anorexic effects of co-morbidities such as pain (Malinauskas *et al*., 2000; Jacob *et al*., 2006), decreased absorption of nutrients, increased degradation and losses of nutrients, increased requirements as a result of elevated basal metabolic rate (Kopp-Hoolihan *et al.*, 1999), and alterations in metabolic pathways.

Good nutrition is essential to promote healthy growth in children with sickle cell disease and may reduce the risk of complications. A balance between minerals and antioxidants is important

in maintaining red cell membrane integrity and function (Khan *et al.*, 2013). Minerals such as copper, zinc, iron, chromium, magnesium, selenium, and antioxidant vitamins like vitamin C and E as well as vitamin A may be needed to perform these protective roles (Lukaski, 2004). Additionally, due to their roles in haemoglobin synthesis and production of red blood cells (Koury and Ponka, 2004; Stover and Field, 2015), adequate status of vitamin B6 and folate will aid the process of compensating for the rapid loss of red blood cells that occurs in SCD patients.

Protein and energy

Protein is an essential macronutrient needed to promote growth in children and synthesise haemoglobin. Children with SCD may require more than the recommended dietary allowance to maintain normal metabolism and physiological processes. This is because higher protein turnover have been reported among SCD patients and this adds an additional nutritional burden (Borel *et al.*, 1998). Although similar energy and protein intakes for both SCD and matched control children have been observed (Singhal et al., 2002), there is consistent evidence of poor growth among SCD children compared to non-SCD (Cox *et al.*, 2011; Mukherjee & Gangakhedka, 2004; Al-Saqladi *et al.*, 2008; Kazadi *et al.*, 2017). Additionally, patients with sickle cell anaemia displayed greater than average requirements for both protein and energy when compared with their sex and age matched peers (Salman *et al.*, 1996). This increased requirement is poorly understood but it has been suggested that hypermetabolism due to shortened life-span of erythrocytes places an increased demand on protein stores, accelerates whole body protein turnover and consequently increases energy expenditure (Reid, 2013). The

most common indicator of poor growth among SCD children is wasting, which is associated with increased hospitalization and poor clinical outcomes. Heyman *et al* (1985) studied five growth-retarded children with HbSS, who were below the fifth percentile for both weight and height. After naso-gastric supplements of protein and calories, in addition to their regular diets, two of the growth retarded children showed improvement and accelerated growth. Although a firm inference of their report is limited due to the small sample size, the results demonstrates that malnutrition is one of the complications of HbSS and that energy and protein supplements could be beneficial for growth in HbSS children. Additionally, .There is some information suggesting that increased dietary requirements as much as needed in pregnancy and growth is necessary to improve clinical outcomes (Hyacinth *et al.*, 2010), although currently, there are no special dietary recommendations for protein and/or energy for patients with SCD.

Polyunsaturated fatty acids (PUFA)

Fatty acids are important components of cell membranes and may play important role in improving and maintaining the overall health and clinical outcomes in patients with SCD. The essential polyunsaturated fatty acids (PUFA), particularly omega-3 and omega-6) are needed to synthesize and repair cell membranes, promote growth of children particularly for neural development and maturation of sensory systems. Blood cell aggregation and adherence to vascular endothelium and inflammation play a central role in vaso-occlusive crisis in sickle cell disease. Omega-3 (n−3) fatty acids (DHA and EPA) have been shown to have anti-aggregatory, anti-adhesive, anti-inflammatory, and vasodilatory properties (Mori and Beilin, 2004). It has therefore been suggested that fatty acids can improve the clinical outcomes of sickle cell patients particularly in the reduction of painful episodes. A double-blinded, olive controlled trial (n = 10,

5 in each study arm) reported a significant decrease in pain episodes among those who received 12% eicosapentaenoic acid (EPA) for one year (Tomer *et al.*, 2001). Similarly, a randomised double-blinded placebo controlled trial among patients with sickle cell anaemia in Sudan reported that treatment reduced the rate of clinical vaso-occlusive events from at least 1 to 0.21 (95% CI: 0.09, 0.47; $P < 0.001$), severe anaemia (3.2% compared with 16.4%; $P < 0.05$) and blood transfusion (4.5% compared with 16.4%; $P < 0.05$) (Daak *et al.*, 2013). There is however, paucity of studies that look at the effects of PUFA on the pathophysiology of children with SCD and the available studies are mostly limited by small sample sizes. The available results however, point to the potential therapeutic benefits of dietary omega-3 fatty acids in SCD. Das (2013) suggests that the positive effect of PUFA supplementation in these studies could be ascribe to the formation of potent anti-inflammatory and anti-aggregatory bioactive lipids such as lipoxins, resolvins, and protectins. There is the need for larger, multi-centre studies that will provide adequate evidence before policies can be formulated regarding PUFA and sickle cell disease.

Micronutrients

Micronutrients are essential vitamins and minerals required for good health. Some micronutrient deficiencies have been associated with sickle cell disease. These include iron, zinc, copper, folic acid, pyridoxine and vitamin E (Hyacinth *et al.*, 2010). Possible mechanisms by which micronutrient deficiency may develop in sickle cell disease include decreased intake, intestinal malabsorption, and increased catabolism of specific nutrients.

Magnesium

Magnesium is the second-most abundant intracellular cation in the body. Magnesium homeostasis is governed by intestinal absorption and renal excretion. Aside its role in stabilizing the structure of ATP in ATP-dependent enzyme catalysed reactions, the macromineral is also vital in neuromuscular transmission and activity. High magnesium intake is associated with greater bone density (Rude and Gruber, 2004) and the mineral is thought to decrease sickle erythrocyte dehydration by diminishing the activity of the K-Cl co-transport pathway, a major factor in the dehydration of erythrocytes in SCD (Brugnara, 1999). In vitro experiments showed that magnesium could decrease sickle cell haemoglobin polymerization by 48% (Nwaoguikpe and Braide, 2012b). Available studies on the level of magnesium (Mg) in sickle cell disease patients have reported conflicting results. Oladipo *et al.* (2005) did not observe any difference in the serum magnesium levels between paediatric SCD cases and controls in Nigeria. Others (De Franceschi et al., 1997; Hankins *et al.,* 2008) have reported reduction in the number of dense erythrocytes and improvement in erythrocyte membrane transport abnormalities as well as increased erythrocyte hydration of patients with SCD on oral magnesium supplements. In a study to determine the effect of magnesium on length of stay for paediatric sickle cell pain crisis, those who received intravenous Mg showed a decrease in the length of hospital stay from approximately five days to an average of three days ($p< 0.01$) (Brousseau *et al.,* 2004). However, the Magnesium for Children in Crises (MAGiC) study conducted among 4-21 year olds with SCD or $S\beta^0$_Thallasemia (Brousseau *et al.,* 2015) showed that intravenous magnesium did not shorten length of hospital stay, nor did it improve the quality of life for the patients. In addition, Goldman *et al.* (2013) reported that although intravenous magnesium was well tolerated in SCD children, there was no difference in the length of stay in the hospital among Canadian children

with SCD. The authors suggested that providing magnesium when crisis has already set in may be too late, but it is possible that oral therapy may prevent the episodes. There is however, lack of information on studies that have looked at the effect of oral magnesium therapy on clinical outcomes. In conclusion, the available evidence intravenous interventions do not support the inclusion of magnesium in the management of SCD.

Iron

Iron is an important trace mineral required for haemoglobin synthesis and proper immune function. Although iron is an important component of red blood cells, excess of it has been shown to contribute to the generation of free radicals, which lead to lipid peroxidation, severe membrane damage and increased haemolysis in sickle cell patients (Pack-Mabien *et al.*, 2015). It has been suggested that diet for sickle cell patients should be low in absorbable iron but high in vegetable proteins. Thus, iron-rich foods, such as liver, iron-fortified formula, iron-fortified cereals, and iron-fortified energy bars should be excluded (Mahan *et al.*, 2012). There are discrepancies in studies from developing and developed countries regarding amount of iron stores in sickle cell patients. While studies from most developing countries have found low iron stores in their sickle cell participants (Okeahialam and Obi, 1982; Vichinsky *et al.*, 1981), the vice versa has been reported in the developed world. This could be explained partly by the lower socioeconomic status among the developing world which leads to a general inadequate intake of dietary intake of iron and subsequent general low iron status in the population.

Although iron deficiency anaemia is a problem in many developing countries, it is often uncommon among patients with sickle cell disease because of increased gastrointestinal

absorption associated with haemolysis and the iron provided by red cell from blood transfusions (Vichinsky *et al.,* 1981). However, it is estimated that about a third of haemolysis that occur in SCA patients is intravascular, resulting in urinary losses of iron and iron deficiency (Koduri, 2003). Iron deficiency may also occur due to repeated phlebotomies and haematuria secondary to renal papillary necrosis. Conversely, SCA patients are at an increased risk of experiencing iron overload. Blood transfusion improves the blood flow by reducing the proportion of red blood cells capable of forming sickle haemoglobin polymers (Little *et al.*, 2010). Additionally, transfusions increase the oxygen-carrying capacity of SCA patients. As such, it is recommended as both prophylaxis and therapy, particularly for stroke (Adams and Brambilla, 2005; Adams et al., 1998). However, transfusion can lead to iron overload (Porter and Garbowski, 2013). Thus iron status needs to be effectively monitored among SCA patients.

Zinc

Zinc is involved in all major aspects of cellular functions including metabolism, detoxification, antioxidant defences, signal transduction, and gene regulation (Bao *et al.,* 2008). Its deficiency can cause physiological defects and cell injury. Manifestations of zinc deficiency include anorexia, skin lesions, growth retardation, neurosensory defects, and immune dysfunction in humans (Prasad, 2008).In the context of sickle cell disease and nutrition, more attention has been focused on zinc than any other mineral. The deficiency of zinc has been reported more among people with 'HbSS' genotype, the most severe form of SCD**.** A study in Nigeria reported that SCD children experiencing painful crisis had lower serum zinc levels compared their counterparts who were in steady condition at time of data collection (Temiye *et al.*, 2011). Also,

zinc deficiency was most common among Canadian children with SCD, and was associated with home pain crises and increased incidence of hospitalization (Martyres *et al.*, 2016). Benefits of zinc supplementation on nutritional indices and anthropometric parameters are well established in literature. In a 12-month, randomized, placebo-controlled trial of zinc supplementation in children aged 4–10 y with SCD-SS, Zemel and colleagues (2002) reported significantly greater increases in height and arm circumference z scores in the zinc group compared to the control. Other anthropometric indices such as height-for-age and weight-for-age z scores also decreased significantly in the control group but did not change significantly in the zinc group. The role of zinc in decreasing oxidative stress and inflammatory cytokines, as well as increasing anti-inflammatory proteins in sickle cell patients has also been documented. Experimentally, the mineral has also been shown to exhibit almost ninety percent inhibition of sickle cell haemoglobin polymerisation (Nwaoguikpe and Braide, 2012a), which is quite high compared to other antioxidants such as vitamins A, E and C. A Cochrane review on this subject indicated that zinc-supplemented SCD patients showed reduction in both frequency of crises and infections (Swe *et al.*, 2013). Thus, available evidence suggests some benefits for SCD patients who receive zinc supplements. However, most of the studies reviewed involved only adults and so multi-center trials that include children will be needed before this can be included in the management of paediatric SCD.

Folic acid

Folic acid is an essential vitamin needed for the production of red blood cells and the formation of neurotransmitters in the brain. As part of routine management of SCD, folic acid is being

prescribed in almost all health centres in both developing and developed countries. It has been recommended that diet for sickle cell patients should be high in folate as needed in much as pregnancy (400 to 600 mcg daily) because of the increased production of erythrocytes needed to replace the cells being continuously destroyed and to prevent megaloblastic erythropoiesis (Mahan *et al.,* 2012). There are however, inconsistencies in literature on both folate status and the clinical benefits of supplementation on the disease manifestations. Some reports have cited low serum and erythrocyte folate levels in paediatric sickle cell patients and high incidence of megaloblastic anaemia (Van der Dijs *et al.,* 2002). The reported positive effects of supplementation of the vitamin include reversal of developmental delay, reduced dactylitis, and reduction of homocysteine levels (Al-Yassin *et al.*, 2012). This subsequently leads to reduced cardiovascular disease, stroke, and venous thrombosis risk. Conversely, others have reported adequate folate status among paediatric patients, as well as subsequent lack of improvement in haemoglobin status, growth characteristics, and infections among patients with SCD after supplementation (Rabb *et al*., 1983). It has been suggested that the observed differences in the findings is due to genetic polymorphisms in folic acid/homocysteine metabolism and inconsistent supplementation doses (Al-Yassin *et al.,* 2012).The limited literature indicates that although folic acid supplementation may increase serum folate level, its effect on anaemia and other symptoms of SCD among children remains unclear (Dixit *et al*., 2016). An important limitation of routine folate supplementation is that it could mask vitamin B12 deficiency in SCD patients, which could lead to the development of neurologic dysfunction (Dhar *et al.*, 2003). This has led some researchers to suggest that routine folate supplementation among SCD should be discontinued. However, this can be addressed by including a consistent monitoring of vitamin

B12 status. A review of literature shows that there is the need for more longitudinal studies with large sample size and longer follow-up periods in this subject area.

Antioxidant vitamins

Vitamin E is the most important lipid-soluble antioxidant in the cell. The vitamin plays an indispensable role in protecting the body against the damaging effects of ROS that are formed metabolically or encountered in the environment. Vitamin C is a nutrient required in very small amounts to perform a range of essential metabolic functions in the body. It is mainly recognised by the role it plays in collagen synthesis which is required for connective tissue formation, as an antioxidant, and the prevention of scurvy. Sickle cell patients are known to be oxidatively stressed and deficient in antioxidant micronutrients (Allard *et al*., 1998). Sickle erythrocytes and their membranes are susceptible to endogenous free-radical-mediated oxidative damage due to chronic redox imbalance in red cells that often results in continuous generation of reactive oxygen species (ROS) with clinical manifestations of mild to severe haemolysis (Nwaoguikpe and Braide, 2012a). The production of ROS can be grossly amplified in response to a variety of patho-physiological conditions such as hypoxia, inflammation, infection, dehydration and deficiency in antioxidant vitamins. There have been reports of low circulating levels of vitamins C and E in SCD patients (Arruda *et al.*, 2013; Bhoi *et al*., 2014; Tukur *et al*., 2015) and increased utilisation of the vitamin for disease process could account for this deficiency. Amer et al. (2006) reported 20-50% lower levels of reduced glutathione (GSH), the major intracellular scavenger of ROS and 10-30-fold higher production of ROS in sickle cell patients compared to Hb AA controls ($p<0.005$). They further showed that exposure of blood samples of sickle cell patients to

antioxidants such as N-acetylcysteine, vitamin C, and vitamin E decreased oxidative stress by 2-fold compared to the control group ($p<0.05$). Other supplementation benefits include in vitro inhibition of formation of dense cells and Heinz bodies (denatured Hb) (Ohnishi *et al.*, 2000). However, a randomised controlled trial that evaluated the effect of vitamins C and E supplementation in adults with sickle cell anemia reported no improvement, but rather an increase in haemolytic markers (Arruda *et al*., 2013). Also, supplementation with these antioxidant vitamins did not reduce lipid peroxidation among SCD patients in Nigeria (Nku-Ekpang *et.al*., 2016). This study also recorded increased activities of scavenging enzymes such as catalase, superoxide dismutase, and glutathione peroxidase. A possible reason for the lack of improvement is the observation that the reduced vitamin E anti-oxidant capacity of SCD was related to transfusion status, but not sickle crises (Marwah *et.al,* 2002). Studies that have had children as the target in this area are not common. Thus, the available evidence do not support the idea that supplementation with vitamins C and E can improve the life of children with SCD.

Vitamin D

Vitamin D is a fat-soluble vitamin responsible for the maintenance of calcium and phosphate homeostasis and is vital for bone health. It is normally referred to as '*the sunshine vitamin*' because modest exposure to sunlight is usually sufficient for its synthesis by the skin. This makes deficiency of the vitamin less a problem in tropical Africa. Deficiency of the vitamin can lead to bone deformities such as rickets in children. It can also result in bone pain, and tenderness (osteomalacia) in adults (Mahan *et al.*, 2012). In reference to sickle cell disease, there is increasing data demonstrating low serum levels of vitamin D among both healthy and sickle cell

children mainly in the developed countries where there is less sunshine. Other possibility may be due to decreased dietary intake and in some cases to seasonal variability in food intake (Hyacinth *et al.*, 2010). A study by Buison *et al.* (2004) showed that HbSS children had a higher risk of low vitamin D status compared to healthy children aged 5-18 years. Similarly, Martyres *et al.* (2016) and Lee *et al.* (2015) found half of their paediatric SCD subjects to be vitamin D deficient, and this deficiency was associated with acute pain. HbSS patients may benefit from routine vitamin D and calcium supplements, to reduce risk of suboptimal peak bone mineral density (BMD) and consequent fragility. Another nutrient intervention documented is the supplementation of high dose of vitamin D to children and adolescents with SCD in a 6 month randomised double blind pilot study to prevent pathologic chronic bone pain (Osunkwo *et al*., 2012). The investigators observed an increase in serum vitamin D among the supplemented group compared with placebo. Additionally, they observed decrease in the number of pain days among the supplemented group compared with the placebo. There is still a need for setting new dietary requirements for vitamin D, based on recent evidence of increased need among healthy individuals, and particularly for HbSS patients who are likely to have even higher than normal requirements for this vitamin (Hyacinth *et al.*, 2010).

Suggested nutritional recommendations for patients with SCD

Although there is sufficient evidence that increased energy expenditure and hypermetabolism increase nutrient requirements among sickle cell patients, there are no specific dietary recommendations for these patients. However, it has been suggested that, SCD patients should

- Take in enough water as possible each day, at least 8–10 glasses to prevent dehydration.

- Avoid caffeine-containing drinks, such as energy drinks, cola or coffee and alcohol. These cause frequent urination which results in dehydration.
- Avoid icy products which could cause blood vessels to narrow, causing difficulty in blood flow through vessels, hence pain.
- Consume protein-dense foods with emphasis on plant-sources of proteins such as beans, peas, pulses, lentils, soybeans, groundnuts, cashew, and mushroom
- Increase consumption of food sources of citrulline, a nutrient that promotes blood vessels relaxation and improves oxygen and blood circulation. Some sources include watermelon, milk, legumes, and cucumber.
- Consume more food sources of folate, vitamin B6, B12, and zinc which are involved in red blood cell production and maintenance of their membrane integrity
- Take iron-rich foods, such as liver, iron-fortified formula, iron-fortified cereals, and iron-fortified energy with caution due to risk of iron overload as well as vitamin C which increases iron absorption (Mahan *et al.*, 2012).

Conclusion

There are indications that children with SCD generally present sub-optimal levels of most nutrients when compared with their non-SCD counterparts. There is however, paucity of information especially from Africa, where the condition is relatively prevalent. For polyunsaturated fatty acids, zinc, folate, and vitamin D, trials with small numbers have suggested potential benefits. However, there is lack of trials with large sample size that support the suggestion that supplementation with various nutrients that have been considered in this review will be helpful. Despite these limitations, dietary supplementations need to be considered as an

integral component of the management of SCD, especially in view of the sub-optimal status of nutrients observed among SCD children. Dietary diversity is a recommended approach to achieving nutritional requirements and adequacy and this may also be beneficial to SCD children. Future studies on the role of diet in the management of sickle cell disease should therefore include this aspect of dietary intake.

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Figure 1: Relationship between infection, malnutrition and pathophysiology of SCD (authors' own construct).