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Malnutrition in Sickle Cell Anemia: Implications for Infection, Growth, and Maturation

Hyacinth I. Hyacinth
Morehouse School of Medicine

Oluwatoyosi A. Adekeye
Morehouse School of Medicine

Christopher S. Yilgwan
Jos University Teaching Hospital

Sickle cell anemia (SCA) is a genetic disease that affects mostly individuals of African and/or Hispanic descent, with the majority of cases in sub-Saharan Africa. Individuals with this disease show slowed growth, delayed sexual maturity, and poor immunologic function. These complications could partly be explained by the state of undernutrition associated with the disease. Proposed mechanism of undernutrition include protein hypermetabolism, decreased dietary intake possibly from interleukin-6-related appetite suppression, increased cardiac energy demand/expenditure, and increased red cell turnover. All the above mechanisms manifest as increased resting energy expenditure. Nutritional intervention utilizing single or multiple nutrient supplementation has led to improved clinical outcome, growth, and sexual maturation. Studies are currently underway to determine the best possible approach to applying nutritional intervention in the management of SCA. Management of SCA will, of necessity, involve a nutritional component, given the sociodemographic distribution of those most affected by the disease, the ease of a nutritional approach, and the wider reach that such an approach will embody.

Keywords: *growth, infection, nutrition, maturation, sickle cell anemia*

Background

Sickle cell anemia (SCA) is a genetic disease that results from the substitution of valine for glutamic acid in the ß-globin chain of the hemoglobin molecule (Pauling & Itano, 1949) and affects mostly people of African or Hispanic descent. The consequence of this amino acid substitution is the

Please address queries to: Hyacinth I. Hyacinth, Department of Microbiology, Biochemistry and Immunology, Morehouse School of Medicine, Atlanta, GA 30310. Email: h.hyacinth@hotmail.com

The corresponding author is currently affiliated with the Medical University of South Carolina in Charleston, SC.

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formation of hemoglobin S (HbS). Under low oxygen tension and/or conditions of acidosis. HbS precipitates and forms polymerized crystals called tactoids (hemoglobin polymers), which distort the red blood cells (Ganong, 2003; Nelson & Cox, 2005). The resulting sickle-shaped red cells lose their pliability and cannot navigate the small capillaries, become sticky, and adhere to the small veins, small arteries, and other blood vessels causing vaso-occlusion (Aster, 2005; Bunn & Forget, 1977). In addition, red blood cells homozygous for HbS (i.e., HbSS) are susceptible to premature destruction, with a red blood cell life span of 8–25 days as opposed to 100–120 days for normal red blood cells (Solanki, McCurdy, Cuttitta, & Schechter, 1988).

Sickle-cell anemia has a high prevalence throughout equatorial Africa; additionally, the genetic defect is now known to be widespread in parts of Sicily and southern Italy, northern Greece, southern Turkey, the Middle East, Saudi Arabia, much of central India, and the Americas (Feldenzer, Mears, Burns, Natta, & Bank, 1979). This wide geographical distribution is thought to be a result of the survival advantage, which the heterozygous genotype (HbAS) confers against malaria infection, causing the genetic defect to persist in the population (Aidoo et al., 2002; Serjeant, 2001) and the movement of people from Africa to other parts of the world. The burden of SCA is highest in sub-Saharan Africa—especially in the West African country of Nigeria, where more than 130,000 (or 19–20:1000) children are born with the disease annually, and approximately 4 million people are afflicted with the disease (Aliyu, Tumblin, & Kato, 2006; Olabode & Shokunbi, 2007; World Health Organization, 1996; World Health Organization, 2006).

In the last few decades, more studies have documented the presence of micro- and macronutrient deficiency among individuals with SCA and their possible association with immunologic (Bao et al., 2008; Fraker, King, Laakko, & Vollmer, 2000; Heyman et al., 1985), nutritional (Gray et al., 1992; Heyman et al., 1985), and growth (Serjeant, Singhal, & Hambleton, 2001; Zemel, Kawchak, Ohene-Frempong, Schall, & Stallings, 2007) abnormalities. Studies using direct measure of nutritional status (Enwonwu & Lu, 1991; Gray et al., 1992; Kennedy et al., 2001; Leonard, Zemel, Kawchak, Ohene-Frempong, & Virginia, 1998; Nelson et al., 2002), indirect assessment of nutritional status (Borel, Buchowski, Turner, Goldstein, & Flakoll, 1998; Buchowski, de la Fuente, Flakoll, Chen, & Turner, 2001; Buison et al., 2005; Henderson, Saavedra, & Dover, 1994; Serjeant et al., 2001; Silva & Viana, 2005), and application of nutritional supplementation (Heyman et al., 1985; Prasad & Cossack, 1984; Waugh, 2005; Williams et al., 2004) have established the association between SCA and the presence of nutritional deficiency among patients with the disease. These studies showed that although intake might be sufficient when measured against the recommended daily dietary allowance for age and sex, it is still insufficient for the individual with SCA due to the increased nutritional demand imposed by the disease. The result is the manifestation of malnutrition-like features (Al-Saqladi, Cipolotti, Fijnvandraat, & Brabin, 2008; Hyacinth, Gee, & Hibbert, 2010; Prasad, 1997).

This review seeks to draw attention to the link between this unapparent nutritional deficit and some observed SCA-related complications. The purpose is to demonstrate that the pathogenesis of some common SCA-associated complications might be related to caloric deficiency,; not caused by inadequate intake, if measured by the standard for individuals without the disease. It further shows that nutrient diversion for propagating and/or compensating for the disease and disease processes might be responsible for the observed undernutrition-like feature of sickle cell disease. Finally, it draws attention to the paucity of research and data on the interaction between nutrition and SCA in humans and the need for further research to understand this relationship and its vital role in the management of the disease.

Sickle Cell Anemia and Undernutrition

Previous studies have hypothesized and documented that SCA leads to a state of undernutrition and poor growth. A hypothesis that has gained traction is that of hypermetabolism. Simply put, hypermetabolism is a state of increased caloric demand with a high rate of catabolism (nutrient breakdown) compared with anabolism (nutrient buildup). In SCA, however, there is a shift toward increased catabolism, leading to increased nutrient demand. Some studies have documented hypermetabolic states among children with SCA (Borel et al., 1998; Hibbert et al., 2006). Hibbert and colleagues (2006) reported that increased myocardial energy demand, along with increased production of proinflammatory cytokines, is associated with increased resting energy expenditure (REE), a surrogate marker of a state of hypermetabolism. Other investigators supported their findings with the observation that, although individuals with SCA may consume diet deemed adequate for a person without the disease, it might be insufficient to maintain normal body function and metabolism, as reflected by delayed growth, slowed maturation, and low weight/height for age (Henderson et al., 1994; Leonard et al., 1998; Silva & Viana, 2005; Zemel et al., 2007); thus, they are in a state of increased energy demand. The shortened life span of sickle red blood cells compared with normal red blood cells (Solanki et al., 1988) explains this finding. The increased destruction of these cells creates a need for increased erythropoiesis (i.e., the process of making red blood cells), which leads to increased protein turnover and thus increased energy demand (Borel et al., 1998; Buchowski et al., 2001; Hibbert et al., 2006; Salman et al., 1996).

Furthermore, increased hemolysis results in decreased red cell count and anemia. As a compensatory mechanism to maintain tissue oxygenation, the heart rate is increased, leading to increased myocardial energy demand (Hibbert et al., 2006; Salman et al., 1996), with the net effect of an increase in myocardial energy requirement and thus total energy requirement. As stated earlier, the patient with SCA is in a state where catabolism exceeds anabolism, resulting in an energy requirement that exceeds the apparently adequate nutrient intake in the absence of SCA. This hypermetabolism has been documented as increased REE, which is a measure of the energy consumption of an individual at rest. Studies show that individuals with SCA have a higher REE compared with age- and sex-matched healthy controls (Akohoue et al., 2007; Barden et al., 2000; Williams et al., 2004). This hypothesis thus posits that hypermetabolism leads to undernutrition because it causes a diversion of nutrients from growth and other required body functions to support the increased requirement for red cell production, increased myocardial energy demand due to increased heart rate (a compensatory mechanism for anemia), and propagation of the state of chronic subclinical inflammation reported among SCA patients (Akohoue et al., 2007; Hibbert et al., 2005; Hibbert et al., 2006).

Another hypothesis states that reduced dietary intake exists in SCA patients, and that the state of undernutrition is due wholly or in part to reduced dietary and energy intake (Fung et al., 2001), with the adequacy of dietary intake decreasing as the individual gets older (Kawchak, Schall, Zemel, Ohene-Frempong, & Stallings, 2007). This hypothesis has not gained as much traction as expected because other studies have reported little to no difference between the dietary and energy intake of children and adults with SCA compared with healthy non-SCA controls (Gray et al., 1992; Heyman et al., 1985; Singhal, Parker, Linsell, & Serjeant, 2002). Despite this, some investigators have posited that repeated ill health and hospitalization might affect the frequency of dietary and energy intake (Hyacinth et al., 2010; Malinauskas et al., 2000). Furthermore, high levels of interleukin-6, a circulating cytokine that is involved in inflammation and host immune defense, has been documented to be associated with appetite suppression and, by extension, decreased dietary intake in cancer patients (Rich et al., 2004; van Lettow, van der Meer, West, van Crevel, & Semba, 2005). Elevated levels of this cytokine have also been reported in SCA patients (Hibbert et al., 2005) and

transgenic SCA mice (Archer et al., 2008). It is believed that the elevated Interleukin-6 levels observed in SCA patients might act to suppress their appetite, reducing dietary and energy intake. In theory, SCA produces a form of protein energy malnutrition due not to poor intake, but to increased energy demand.

Implication for Infection

Infections occur as a complication of SCA. These patients are particularly prone to infection with encapsulated organisms because of the occurrence of autosplenectomy from repeated subclinical splenic infarction associated with this disease (Aster, 2005). In addition, lower serum immunoglobulin M levels, impaired opsonization, and sluggish alternative complement pathway activation further increases susceptibility to other common infectious agents, such as *Mycoplasma pneumoniae*, *Salmonella typhimurium*, *Staphylococcus aureus,* and *Escherichia coli*. Low serum immunoglobulin level is a widely documented feature of malnutrition, thus malnutrition from increased demand reported in patients with SCA can also account in part for their increased susceptibility to infection (Fock, Vinolo, de Moura Sá Rocha, de Sá Rocha, & Borelli, 2007; Hughes et al., 2009; Katona & Katona-Apte, 2008; Lesourd & Mazari, 1997), similar to what has been described in children with non-SCA-associated malnutrition. These studies show that non-SCA children and mouse models with protein energy malnutrition have impaired immune response to infection and/or challenge with a component (lipopolysaccharide) of an infectious organism (Fock et al., 2007; Hughes et al., 2009), as seen among children with malnutrition due to SCA. Serjeant (2005) reported that septicemia among African SCA patients has been documented as being from organisms other than *Streptococcus pneumoniae*, making traditional intervention to reduce mortality (Cummins, Heuschkel, & Davies, 1991; Gaston et al., 1986; John et al., 1984) less effective. This increased susceptibility to non-pneumococcal septicemia could be explained in part by the prevalence of malnutrition in this region and a further increased prevalence among individuals with SCA. In addition, the state of nutrient and energy deficiency caused by SCA could lead to increased susceptibility, consequent upon a depressed immune system and response.

Studies in the last 2 decades using dietary supplement in patients (children and adults) with or without SCA had reported—in addition to improved growth—a decrease in the incidence of infection among the patients receiving these supplements (Bao et al., 2008; Heyman et al., 1985; Lesourd & Mazari, 1997; Prasad et al., 2007; Salman et al., 1996). This evidence demonstrates a clear association between the increased incidence of infection among patients with SCA and their "state of [undernutrition]." Zinc, an often deficient nutrient in patients with SCA (Khan, Trottier, & Naydenov, 2009; Leonard et al., 1998; Prasad, 2002), is also linked with increased risk for infection when deficient, with supplementation resulting in a decrease in the incidence of infection (Bao et al., 2008; Bhutta et al., 1999; Muskiet, Muskiet, Meiborg, & Schermer, 1991; Prasad et al., 2007; Sazawal et al., 1998).

Implication for Growth and Maturational Abnormality

Growth and maturation is affected by SCA, resulting in growth retardation (Henderson et al., 1994; Heyman et al., 1985) and slowed maturity (Serjeant et al., 2001). Children with SCA attain maturational milestones such as menarche or adrenarche significantly later than their age- and sex-matched peers without SCA (Zemel et al., 2007). Their growth is also compromised as a result of diversion of nutrient from buildup of tissues, in favor of the provision of energy for increased myocardial demand, propagating inflammation and replenishing red blood cells, which are constantly being hemolyzed (Hibbert et al., 2006). Studies using dietary supplementation in humans with SCA (Heyman et al., 1985; Ohnishi, Ohnishi, & Ogunmola, 2000; Waugh, 2005; Williams et al.,

2004; Zemel, Kawchak, Fung, Ohene-Frempong, & Stallings, 2002) and mouse models of human SCA (Archer et al., 2008; Dasgupta, Hebbel, & Kaul, 2006; Fasipe, Ubawike, Eva, & Fabry, 2004; Kaul, Zhang, Dasgupta, & Fabry, 2008) have reported various benefits of nutritional supplementation.

Delayed growth and maturation among individuals with SCA is associated with low plasma zinc (Leonard et al., 1998), which is also associated with low levels of serum testosterone among males (Prasad, 2008; Sandstead et al., 1967) and decreased pubertal development in general (Leonard et al., 1998). Investigators have demonstrated that providing micronutrient supplements to individuals with SCA led to improvement in growth and maturation by way of improved serum testosterone levels. Parasad and Cossack (1984), as well as Zemel and colleagues (2002), demonstrated that administering zinc supplements to growing children with SCA led to improvement in growth. Supplementing other micronutrients like vitamin A (Schall, Zemel, Kawchak, Ohene-Frempong, & Stallings, 2004), vitamin B, and magnesium (De Franceschi et al., 2000) resulted in clinical benefits such as improved growth, decreased hospital emergency room visits, decreased frequency of pain crisis, and reduced frequency of infection. It also led to improvement in muscle function, cognition, and coordination; decreased inflammation; and improvement in antioxidant and anemia status. These results, apart from demonstrating the benefits of nutrition in the management of SCA, provide further support to the hypothesis that some SCA-associated complications have as much nutritional underpinning as they do genetic.

Nutritional Intervention to Manage Sickle Cell Anemia

As earlier mentioned, several attempts have been and are being made to correct the nutritional deficiency in SCA in order to improve growth (Heyman et al., 1985; Prasad & Cossack, 1984), body composition (Zemel et al., 2002), and vascular and immune function (Kaul et al., 2008; Peranzoni et al., 2008); compensate for the hypermetabolism associated with the disease (Williams et al., 2004); and decrease inflammation (Archer et al., 2008; Dasgupta et al., 2006); among other improvements . The great majority of these have been single-nutrient supplementation, with mixed results (Hyacinth et al, 2010). A few have utilized a combination of nutrients, with really impressive results even with a small sample size (Chan, 2000; Heyman et al., 1985; Ohnishi et al., 2000, Hibbert, Stiles, Umeakunne, & Hyacinth, 2011). Some researchers believe that an approach that utilizes a combination of nutrients (macro- and micronutrients) is likely to produce the best results (Chan, 2000; Ohnishi et al, 2000; Hyacinth et al., 2010). These investigators suggested that because nutrient utilization in the body is a multistep process, with different nutrients feeding into the process at various points, insufficient quantities of one component of this multistep process could have a deleterious (Chan, Chow, & Chiu, 1999) effect on the entire body. Chan (2000) proposed that an antioxidant will end up producing reactive oxygen species and, thus, oxidant stress if adequate quantity of the antioxidant agent was not given ab initio. It was reasoned that in the absence of more antioxidant nutrients, the oxidized form of the initially administered antioxidant ends up propagating the oxidant damage it was administered to prevent.

Future Directions in Finding a Nutritional Remedy for Sickle-Cell-Anemia–Associated Undernutrition

Currently, there are few ongoing pilot clinical trials in the United States with the aim of identifying nutritional approaches to managing SCA, using a combination of macro and micro nutrients (Hibbert et al, 2011) to provide additional calories in a low-bulk but high-calorie format that is appealing to children. Some approaches use single macro or micro nutrients or a combination of micro nutrients. An example is the recently published vitamin D study (Osunkwo et al, 2012) conducted at Emory University. In this study, the investigators provided vitamin D supplement to children with SCA in

order to prevent some of the pathologic bone changes observed in these patients. They reported an increase in serum vitamin D and vitamin D precursor level among the supplemented group compared with placebo. Additionally, they observed a decrease in the number of pain days and an increase in the quality-of-life scores among the supplement compared with the placebo group. As described by Ohnishi and colleagues (2000) and Chan (2000), a combined nutritional approach is most appropriate because the combination of antioxidants exhibit a synergistic effect, and we expect the same effect on improvement in health outcomes for individuals with SCA from an interaction between macro and micro nutrients when administered at the same time by the same nutritional supplement. With that in mind, our center designed and carried out a pilot clinical trial, which adopted an approach that utilizes a combination of both micro and macro nutrients. The supplement developed at our center will provide additional calories equal to 40% of that recommended for age and sex to the normal daily dietary intake of the individual. This ensures that the extra caloric requirement due to the pathological processes of the disease is adequately compensated for.

Additional funding is needed to enable further studies. Priority needs to be afforded this area of SCA research, as it has the potential to address more than one problem (malnutrition in general, maternal mortality, and child mortality), in addition to addressing the complications of sickle cell disease. Multicenter studies that would enable the understanding of the relationship between nutrition and SCA, in addition to informing patient care, can only be conducted with improved funding. Although a lot has been learned from mouse models (Archer et al., 2008; Dasgupta et al., 2006; Kaul et al., 2008; Capers et al., 2010; Romero, Suzuka, Nagel, & Fabry, 2002), our recent work (yet to be published) indicates that the dietary requirements are different. For example, while a normal balanced human diet contains 12–15% of calories from protein, that of mice contains about 20% of calories from protein. Furthermore, mice with SCA have other hematological and pathological features that are different from what has been described among humans with SCA (Manci et al., 2006). This necessitates additional funding to enable more robust human studies, although it should still be informed by data from studies using mouse models.

Sickle-cell-anemia–associated complications such as stroke and acute chest syndrome are being managed using chronic packed red blood cell transfusion and hydroxyurea. Results from the Stroke Prevention in Sickle Cell Anemia (STOP) trial, Hydroxyurea to Prevent Organ Damage in Children With Sickle Cell Anemia (also known as the Pediatric Hydroxyurea Phase III, or BABY-HUG, clinical trial), and Pediatric Hydroxyurea in Sickle Cell Anemia (PED HUG or HUG-KIDS) clinical trial all suggest these approaches alone are unable to promote growth and maturity to any appreciable level (Adams et al., 1998; Thompson et al., 2010; Wang et al., 2002). It is the position of the authors, however, that if these interventions were coupled with additional caloric supplementation, the results might be different. This is because neither packed red blood cell transfusion nor hydroxyurea provide any appreciable decrease in caloric need or provide any appreciable amount of added calories for patients with sickle cell disease.

Finally, the importance of finding a nutritional remedy lies in the fact that currently available approaches for managing sickle cell disease are either too expensive and not readily accessible (e.g., bone marrow transplantation) or have side effects, such as alloimmunization and iron overload in the case of blood transfusion and potential risk for malignancy in the case of hydroxyurea. Furthermore, it will be essential for more studies to adopt a nutritional approach as a part of the management modality for SCA in the light of the fact that more than two-thirds of the patients with SCA live in areas of the world with low socioeconomic status and have little to no means of accessing the aforementioned management approaches.

Conclusion

Sickle cell anemia still remains a devastating global disease that reduces the life expectancy of millions of children of African descent. It is a serious cause of health disparity between countries and between races within the same country. Many complications associated with the disease have a nutritional underpinning. Addressing this problem requires further—and larger—multicenter studies that will enable the development of a tailored daily dietary requirement for individuals (children, adults, and pregnant women) with SCA. Additionally, multinational collaboration is required in order to identify the differences in caloric requirement that might exist between individuals with SCA residing in developed, developing, and emerging-economy countries. Finally, a nutritional approach for the management of this disease holds a lot of promise for improving the clinical outcome, quality of life, and future prospects of those with SCA.

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