

Understanding Growth Failure in Children With Homozygous Sickle-Cell Disease

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Abstract

Sickle-cell disease is the most prevalent genetic hematologic condition in the United States. Numerous studies have demonstrated poor growth and delayed maturation in children with homozygous sickle-cell disease; however, the pathophysiology remains inadequately understood. Affected children have normal weight and length at birth, and then around 6 months of age their growth patterns begin to diverge from the norm. The growth deficits experienced by these children remain a problem with clinical significance and intangible consequences. A review of literature has provided insight into the multifactorial basis of the growth failure experienced by this population. It is important that nurses and health care providers are familiar with the growth patterns unique to sickle-cell disease and recognize their role in clinical practice.

Keywords

sickle-cell disease, growth, nutrition

Overview of Sickle-Cell Disease

Sickle-cell disease (SCD) is a chronic, genetically inherited hemoglobinopathy caused by a point mutation in which valine replaces glutamic acid at the sixth position of the β -globin chain on chromosome 11. The mutation results in the production of sickle hemoglobin (Hb S), which differs from normal hemoglobin (Hb A) by its polymerization into a fragile and sickled shape under altered conditions. While in utero, fetal hemoglobin (Hb F) is the most abundant type. Shortly after birth, and possibly even during the later months of gestation, the amount of circulating Hb F diminishes and Hb A replaces it. Once the transition from fetal to adult hemoglobin is nearly complete, individuals with sickle cell begin to experience the sequelae of their disease. There are 4 major genotypes of SCD: SS, SC, β^+ , and β^0 . Homozygosity for the sickle mutation, also known as sickle-cell disease SS (SCD-SS), is the most prevalent and severe variant (Frenette & Atweh, 2007). Clinical manifestations of SCD-SS include, but are not limited to, chronic hemolytic anemia, vaso-occlusive episodes, splenic sequestration, cerebral vascular accident, and disturbances in growth and development (Ballas et al., 2010).

The National Institutes of Health reports that SCD affects 1 in every 500 African American births and 1 in every 36 000 Hispanic American births. It is estimated

that 2 million Americans are carriers of the sickle-cell trait, occurring at an incidence of 1 in 12 African Americans (Center for Disease Control, 2010). The high prevalence of the disease and its improved survival dictate the need for increased understanding of its potentially modifiable manifestations.

Growth Failure in SCD

Two terms are commonly used to describe poor growth in childhood. Failure to thrive describes children who have height, weight, and head circumference that do not match standard growth charts. The child's weight falls lower than the third percentile or 20% below the ideal weight for his or her height. Growth velocity may have plateaued or fallen after a previously established curve (Kaneshiro & Zieve, 2009). Growth failure describes a linear growth rate below the appropriate velocity for age (Kemp & Gungor, 2009). Anthropometric Z scores are used to statistically present height/length-for-age, weight-for-age, body mass index (BMI)-for-age, and weight-for-height. Table 1 displays normal linear growth rates for children.

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Table 1. Normal Linear Growth Rates for Children

Developmental Period	Expected Growth
Infant (0-12 months)	9-11 in./year or 23-28 cm/year
Toddler (12-36 months)	3-5 in./year or 7.5-13 cm/year
Child (3 years-puberty)	2-2.5 in./year or 5-6.5 cm/year

Children with SCD-SS are often affected by failure to thrive and growth failure as evidenced by significantly decreased height, weight, and BMI in comparison with standardized growth charts. Zemel, Kawchak, Ohene-Frempong, Schall, and Stallings (2007) report that “most children with SCD experience growth failure at some point” (p. 611). Their skeletal age is delayed an average of 1.4 years (Zemel et al., 2007). They also experience delayed sexual development when compared with healthy controls (Ballas et al., 2010). A systematic review of growth and nutritional status in children with homozygous sickle cell described a “consistent pattern of growth failure among affected children from all geographic areas, with good evidence linking growth failure to endocrine dysfunction, metabolic derangement, and specific nutrient deficiencies” (Al-Saqladi, Cipolotti, Fijnvandraat, & Brabin, 2008, p. 165).

A longitudinal study conducted by Zemel et al. (2007) demonstrated that 84% of children with SCD-SS experienced decline in one or more indicators of growth over a 4-year period. “The prevalence of growth failure was age dependent and worsened with age in most subjects” (Zemel et al., 2007, p. 611). More severe growth deficits have been observed in males with SCD when compared with females. Males are more likely than females to have growth failure in all 3 measures of weight, height, and BMI.

The purpose of this article is to explore the patterns of growth in children and adolescents with SCD, as well as to gain insight into the multifactorial causes of growth failure. Although the focus of this article is growth failure, weight and BMI will be referred to frequently as each measurement contributes to the overall growth of a child. Physical maturation is briefly described as it represents the continuum of growth through adolescence.

Delayed Physical Maturation in SCD

The pattern of declining growth in children with homozygous SCD continues throughout childhood and adolescence for males. Females experience a degree of catch-up growth in their height and weight with the onset of puberty. Both genders progress through puberty slower than matched healthy controls (Rhodes et al., 2009). Studies show that puberty is delayed 1 to 2 years in adolescents with SCD

(Zemel et al., 2007). The median age of menarche is 13.2 years; the delay is related to low-weight status (Zemel et al., 2007). The median age of females in Tanner stages II to IV for breast and pubic hair development is 1 to 2 years delayed compared with healthy non-Hispanic black children (Zemel et al., 2007). A similar delay in genital and pubic hair development has also been observed in males (Zemel et al., 2007). Significantly smaller testicular volume and lower testosterone concentrations have also been noted (Smiley, Dagogo-Jack, & Umpierrez, 2008).

Literature Review

Methods

An extensive literature search was conducted to examine the etiology of growth failure in children with homozygous SCD. The electronic databases searched include Cochrane, Medline/PubMed, and Cinahl. Search terms used SCD combined with homozygous, growth, height, weight, body mass index, and nutrition.

Growth Failure

There are 4 main factors that have been found to contribute to growth failure in children with homozygous SCD: endocrine dysfunction, inadequate nutritional intake, micronutrient deficiencies, and hypermetabolism.

Endocrine Dysfunction

It has recently been proposed that the growth failure experienced by children with SCD-SS is partly related to alterations in the insulin-like growth factor I axis (Collett-Solberg, Fleenor, Schultz, & Ware, 2007). Abnormalities in the GH-IGF-I-IGFBP3 (growth hormone-IGF-I-IGF-binding protein 3) axis have been linked to the impaired growth in SCD (Smiley et al., 2008). Affected children whose height is below the 25th percentile for age have significantly decreased serum IGF-I concentrations compared with children with constitutional short stature (Smiley et al., 2008). Decreased synthesis of IGF-I may be secondary to a disturbed GH-IGF-I axis, undernutrition, or the hypermetabolic state of the disease (Smiley et al., 2008).

Inadequate Nutritional Intake

Suboptimal nutritional intake has been correlated with the poor growth commonly seen in children with SCD-SS (Kawchak, Schall, Zemel, Ohene-Frempong, & Stallings, 2007). Although the etiology of this inadequate intake

is not completely understood, studies have demonstrated the prevalence of anorexia following vaso-occlusive pain episodes. Dietary intake can be markedly reduced prior to hospital admission and remain suboptimal for weeks (Al-Saqladi et al., 2008).

A 3-year prospective study using dietary recall characterized nutrient intakes expressed as percent dietary reference intakes and found that the intake of vitamins D and E, folate, calcium, and fiber was suboptimal for the total sample of children with SCD-SS. As high as 85% of children fell below the estimated average requirement. Intake of riboflavin, zinc, calcium, magnesium, and phosphorus declined significantly with age. Children with SCD-SS had poorer nutrient intake than children matched for age and race in the National Health and Nutrition Survey (NHANES III; Kawchak et al., 2007).

Micronutrient Deficiencies and Low Bone Mineral Density (BMD)

Studies have been conducted to exclusively examine the status of vitamin D, vitamin A, and zinc in the SCD population. Although other micronutrients have been found to be lacking, this article focuses specifically on these 3 as they each play an essential role in healthy growth.

Vitamin D studies have linked suboptimal levels to poor calcium absorption and low BMD. A study by Buisson et al. (2004) found that 65% of children with SCD-SS had 25-hydroxyvitamin D (25-OHD) levels significantly lower than healthy Black children. It was noted that the children with low vitamin D status consumed significantly less vitamin D and calcium than children with normal levels (Buisson et al., 2004).

A common sequela of insufficient vitamin D is low BMD. Vitamin D is needed to promote calcium absorption in the gut and maintain adequate serum calcium and phosphate concentrations to enable bone mineralization. Low BMD and subsequent failure to attain optimal peak bone mass during growth in childhood may lead to the development of osteoporosis (Fung et al., 2008). A study that used dual-energy X-ray absorptiometry found that BMD was reduced in 64% of the children with SCD-SS (Lal, Fung, Pakbaz, Hackney-Stephens, & Vichinsky, 2006). This finding was associated with deficient calcium intake and low serum vitamin D levels in children. There was no association between low BMD and gender or transfusion status (Lal et al., 2006).

A study examining vitamin A status in children with SCD-SS revealed that the mean serum retinol level was suboptimal in 66% of the children (Schall, Zemel, Kawchak, Ohene-Frempong, & Stallings, 2004). Compared with those with normal levels, children whose levels were suboptimal had significantly lower BMI Z

scores, lower hemoglobin and hematocrit levels, as well as increased hospital stays (Schall et al., 2004).

Zemel, Kawchak, Fung, Ohene-Frempong, and Stallings (2002) conducted a study to determine the effects of zinc supplementation on growth and body composition in children with SCD-SS. There were no changes in growth and body composition of participants at baseline; however, after 12 months the sample of children receiving zinc had significantly greater mean increases in height and arm circumference Z scores. Height and weight for age Z scores significantly decreased over 12 months in the placebo group but remained unchanged in the zinc group. The baseline dietary intake of zinc was not significantly different between the zinc and control groups (Zemel et al., 2002).

The results of these studies examining vitamin D, vitamin A, and zinc status suggest that increased nutritional demands are likely contributing factors to the micronutrient deficiencies seen in SCD-SS. Affected children may be unable to meet requirements through dietary intake alone (Buisson et al., 2004; Schall et al., 2004).

Hypermetabolism

Hibbert et al. (2006) conducted research to explore the erythropoiesis and myocardial energy requirements that contribute to the hypermetabolism of SCD. Asymptomatic children with SCD were found to have a 52% higher protein turnover rate. Protein turnover is an energy-consuming process. Proportional reticulocyte count, hemoglobin synthesis rate, myocardial oxygen consumption, and resting energy expenditure were also found to be significantly higher than in healthy unaffected controls. The results of these studies demonstrate that the metabolic demands of increased erythropoiesis and cardiac energy consumption account for much of the excess protein and energy metabolisms in children with homozygous SCD (Hibbert et al., 2006).

Al-Saqladi et al. (2008) report that the resting metabolic rate is 19% higher in children with homozygous SCD than in African American controls. The difference is not related to the size of lean body mass. These data suggest that by reducing the hemolysis of sickled red blood cells and the erythropoietic protein turnover rate, hemoglobin concentration would be increased and may result in improved growth.

Research conducted using the results of the Stroke Prevention Trial for sickle-cell anemia (STOP) study found a significant improvement in the growth of children receiving chronic transfusion therapy (Wang et al., 2005). Participants of the STOP trial received packed red blood cell transfusions every 3 to 6 weeks, and hemoglobin S levels were maintained at 30% pretransfusion for

approximately 2 years. Serial height, weight, BMI, and growth Z scores were measured every 3 months throughout the trial. After 24 months of transfusion, the Z scores for height, weight, and BMI had improved significantly (Wang et al., 2005).

In the absence of chronic transfusion therapy, males have lower hematocrit and hemoglobin F levels than females (Zemel et al., 2007). Silva and Viana (2002) compared 100 children with SCD with the National Center for Health Statistics reference population. After 1 year of study, male children with SCD had a significant decrease in weight-for-age and height-for-age Z scores. The lower mean Z scores were observed among patients with lower hemoglobin concentrations and consequently higher reticulocyte counts. Hemoglobin, hematocrit, and hemoglobin F concentrations are higher in girls, who did not experience significant decreases in Z scores over time (Silva & Viana, 2002). The reason for this gender difference is unknown.

The knowledge gained through both the STOP trial and the study by Silva and Viana (2002) supports the suggestions made by Hibbert et al. (2006), by concluding that the reduced hemolysis of sickled red blood cells and higher hemoglobin concentration that results from chronic transfusion therapy may improve growth by lowering energy expenditure.

Implications for Nursing Practice

Growth Monitoring

Zemel (2009) notes that “the growth failure and delayed maturation of children with SCD are not disease characteristics, but are secondary effects of the severe anemia that may improve with advances in clinical care” (p. 500). It is imperative that growth failure and delayed maturation are recognized as treatable effects and not as “symptoms.” The child with SCD encounters many different health care providers participating in his or her care. It is the role of these health care providers to ensure that all children are receiving properly measured and calculated height, weight, and BMI at regular intervals. Growth velocity and BMI must be recorded on the appropriate growth chart issued by the National Center for Disease Control each time they are measured. The school nurse, registered bedside nurse, advanced practice nurse, and primary and specialty care providers equally share this responsibility for a child’s growth. It is through serial measurements and plotting that care providers can track growth curves and recognize and respond to growth failure and poor weight gain.

It is a well-known anecdotal finding that children with a chronic disease requiring regular “sick-visits” and

hospitalizations may not have their growth measured as frequently as healthy children who visit their primary care practitioner for annual “well-child” checkups. Children who present to their primary care practitioners with an acute illness certainly should, but do not always, have their height, weight, and BMI plotted. In time, repeated sick-visits develop into months or years without any documentation of growth.

The child admitted to the hospital with homozygous sickle cell is likely to be experiencing an acute manifestation of his or her disease. It is at times like these that the bedside nurse, advanced practice nurse, and physician may certainly overlook measurements of growth. It must be remembered that in spite of chronic disease, growth is the number one indicator of the overall health and well-being of a child. The medical team must be able to recognize the onset of growth disturbances in this population and advocate for the affected child’s optimal nutrition. Children who are showing early signs of compromised growth warrant a nutritional assessment and counseling.

It is important to be aware of the findings that identify a child at risk for undernutrition when assessing a growth chart: weight or height less than the fifth percentile in any age group, BMI less than the fifth percentile in children 2 to 20 years, and weight-for-length less than the fifth percentile in children from birth to 36 months.

To identify these risks, it is essential that children be measured at frequent and appropriate intervals. Table 2 lists the ideal frequency of growth assessments for children in an inpatient setting. These are the recommendations in place at The Children’s Hospital of Philadelphia. Other institutions may slightly differ. These guidelines are not specific to children with sickle cell or other chronic diseases.

Table 3 portrays the recommended frequency of outpatient well-child growth assessments. These are the recommendations put forth by the American Academy of Pediatrics (2008) and are not specific to children with SCD. Children with SCD would benefit from an even greater frequency of growth assessment; however, such guidelines are not available in the published literature.

The advent of electronic medical record charting with automatically calculated Z scores and BMI has aided in the ability of health care providers to visualize growth velocity at various intervals of time; however, this form of charting is not available to every institution and it still requires that the measurements be manually obtained and entered. Therefore, the responsibility continues to lie within the hands of the child’s entire health care team to make certain that patients do not receive a less than complete assessment of this fundamental component of health and well-being in childhood.

Table 2. Frequency of Growth Assessments in the Inpatient Setting

Age	Weight	Length/Height
Preterm infant	Daily	Weekly
Term infant-12 months	Twice weekly	Monthly
12-24 months	Weekly	Monthly
2-20 years	Weekly	Monthly

Table 3. Frequency of Growth Assessments in the Outpatient Setting

Age	Weight	Length/Height
Birth-2 months	Every month	Every month
2-6 months	Every 2 months	Every 2 months
6-18 months	Every 3 months	Every 3 months
18 months-3 years	Every 6 months	Every 6 months
3-21 years	Every year	Every year

Nutritional Assessment and Prevention

The review of literature supports the presence of micro-nutrient deficiencies and suboptimal nutritional intake in the pediatric SCD-SS population. Many studies describe the need for health care providers to optimize the nutritional status of affected children in an effort to improve growth outcomes. There is evidence that nutrient supplementation given via the nasogastric route to affected children with growth failure and failure to thrive can result in a rapid and sustained increase in growth (Al-Saqladi et al., 2008). There have been few nutritional supplementation studies done on the SCD population; however, this finding supports the benefit of increasing fat, protein, and carbohydrate intake.

It is the role of both the registered nurse and advanced practice nurse to carefully assess and evaluate children's nutritional intake and make healthy, well-balanced food choice suggestions that nurture growth and development. Vitamin and mineral deficiencies including vitamin D, calcium, vitamin A, and zinc should be especially considered when evaluating diet and making recommendations.

Vitamin D is a fat-soluble vitamin that is naturally present in very few foods. It is added to several foods such as vitamin D-fortified milk and other dairy products. It is produced endogenously when ultraviolet rays from sunlight make contact with the skin and trigger vitamin D synthesis (National Institutes of Health [NIH], 2009c). Vitamin D is essential for promoting calcium absorption in the gut and maintaining adequate serum calcium and phosphate concentrations to enable normal bone mineralization (NIH, 2009c). Its absorption is crucial in preventing rickets in children. The American Academy of

Table 4. Adequate Intakes for Calcium

Age (Years)	Daily Calcium (mg)
1-3	500
4-8	800
9-18	1300

Pediatrics recommends that all children age birth to 18 years receive 400 IU of vitamin D per day (Wagner & Greer, 2008). The American Academy of Pediatrics also recommends that older children and adolescents who do not obtain 400 IU/day through vitamin D-fortified milk and foods should take a 400-IU vitamin D supplement daily (Wagner & Greer, 2008).

Calcium, the most abundant mineral in the body, is required for muscle contraction, blood vessel expansion and contraction, secretion of hormones and enzymes, and transmitting impulses throughout the nervous system (NIH, 2009a). Less than 1% of total body calcium is needed in the blood to support these functions; however, it is vital that this level be maintained (NIH, 2009a). The remaining 99% of the body's calcium is stored in the bones and teeth where it supports their structure. There is constant reabsorption and deposition of calcium into new bone, striving to maintain an ideal BMD (NIH, 2009a). Calcium is provided in the diet by dairy products and some vegetables including cabbage, kale, and broccoli. Many fruit juices for children as well as some cereals are fortified with calcium (NIH, 2009a). Table 4 displays the recommendations for adequate calcium intake put forth by the NIH.

Vitamin A is an important group of compounds necessary for bone growth as well as vision, reproduction, cell division, and cell differentiation (NIH, 2006). It also helps prevent bacterial infections by promoting healthy linings of the eyes, respiratory tract, intestinal tract, and urinary tract (NIH, 2006). It can be found in both plant and animal sources. It is provided in the diet by many vegetables, meats, dairy products, and fortified foods such as certain cereals (NIH, 2006). Table 5 displays the NIH recommended dietary allowances for Vitamin A.

Zinc is involved in many aspects of cellular metabolism and plays an important role in growth and development during childhood and adolescence. It also assists in proper immune function (NIH, 2009b). It is provided through the diet in a variety of foods including red meat, poultry, beans, nuts, whole grains, fortified cereal, and dairy products. The body does not have any means of storing zinc; therefore, daily dietary intake is required to maintain a steady level (NIH, 2009b). As there have been studies to improve the growth of children with SCD, it is important to evaluate daily intake in this population and discuss the possibility of supplementation with the

Table 5. National Institutes of Health Recommended Dietary Allowances for Vitamin A

Age (Years)	Daily Vitamin A (IU)
1-3	1000
4-8	1320
9-13	2000
14-18	Males, 3000; females, 2310

Table 6. National Institutes of Health Recommended Dietary Allowances for Zinc

Age	Daily Zinc (mg)
7 months-3 years	3
4-8 years	5
9-13 years	8
14-18 years	Males, 11; females, 8

medical team. Table 6 displays the NIH recommended dietary allowances for zinc.

Anticipatory Guidance

Another important role of the nurse practitioner is to provide anticipatory guidance to both children and adolescents with SCD. Education should include an explanation of the impact that SCD has on their growth and development and prepare preadolescents for a probable delay in puberty.

It would be beneficial for children to know the findings that some studies have presented, including vitamin and mineral deficiencies, slower progression through puberty, catch-up growth for females, and poorer linear growth experienced by males.

Preadolescents should be informed that puberty is generally delayed 1 to 2 years and skeletal age is delayed 1.4 years (Zemel et al., 2007). Females should be taught not to expect menstruation as early as their peers. It is important to explain to them that based on research that has been done on other girls with SCD, the average age of menarche is 13 years (Zemel et al., 2007). Males should be counseled on the fact that they may not grow as tall as their peers. It should be explained that this is because of several factors including a lower hemoglobin level that causes the body's energy to be used up faster.

In terms of sexual development, adolescents tend to crave answers to the question, "Am I normal?" By providing anticipatory guidance about the physical growth and development tendencies of their disease, adolescents can be made to better understand their bodies and expect the growth variants that their SCD entails.

Summary

The Centers for Disease Control estimates that 70 000 to 100 000 people are currently living with SCD in the United States (NHLBI, 2010). Both the high prevalence of this disease and its improved survival rates dictate the need for better understanding of its potentially modifiable manifestations in childhood. It is well studied that infants with SCD-SS have a normal weight and length from birth until around 6 months of age and then proceed to exhibit a deviation from the national standard. The complex etiology of this growth pattern is not well understood; however, advances in research have unveiled a multifactorial basis for its occurrence.

Scientific evidence supports the presence of nutritional deficiencies and suboptimal nutritional intake in the pediatric SCD-SS population. Research has discovered that increased nutritional demands due to factors causing hypermetabolism are a likely culprit of this finding. These studies introduce the compelling need for health care providers to optimize the nutritional status of patients in an effort to improve growth outcomes.

The dawn of chronic transfusion therapy initiated by the STOP trials has provided us with insight into the hemolytic component of growth deficits. It is known that children who receive chronic red blood cell transfusions have better growth. The reduced hemolysis of sickled cells along with higher hemoglobin concentrations results in lower energy expenditure. It is also known that among children with SCD-SS not receiving transfusion therapy, males have lower hematocrit and hemoglobin F levels than females. Numerous studies have demonstrated that males are more likely than females to have growth deficits in all measures. During puberty, growth in males continues to decline whereas females experience a degree of catch-up growth.

The negative consequences that poor growth during childhood has on one's health are many. The inability to maintain a proper growth velocity can result in delayed puberty and menarche, skeletal delay, low BMD, and osteoporosis later in life. These physical manifestations of poor growth are quantifiable; however, the inherent psychosocial impact is not. Children living with SCD suffer from many adverse sequelae including frequent hospitalizations, painful vaso-occlusive episodes, chronic anemia, and more. Many of the disease manifestations are only "treatable," as medications and blood cell transfusions cannot provide a permanent fix. The medical team must be cautious. They must take care so as not to inadvertently overlook indications of poor growth. These less obvious factors are ones that can provide great insight into the "big picture" of a child's overall health. Although ongoing data collection at the research

level is critical, so is the need for earlier recognition of growth disruption in these children at the clinical level. Facilitating early recognition by following the clinical implications described above can lead to proper nutritional interventions and improved health outcomes in the future.

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Bio

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