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Growth and nutritional status of children with homozygous sickle cell disease

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Abstract

Background: Poor growth and under-nutrition are common in children with sickle cell disease (SCD). This review summarises evidence of nutritional status in children with SCD in relation to anthropometric status, disease severity, body composition, energy metabolism, micronutrient deficiency and endocrine dysfunction.

Methods: A literature search was conducted on the Medline/PUBMED, SCOPUS, SciELO and LILACS databases to July 2007 using the keywords sickle cell combined with nutrition, anthropometry, growth, height and weight, body mass index, and specific named micronutrients.

Results: Forty-six studies (26 cross-sectional and 20 longitudinal) were included in the final anthropometric analysis. Fourteen of the longitudinal studies were conducted in North America, the Caribbean or Europe, representing 78.8% (2086/2645) of patients. Most studies were observational with wide variations in sample size and selection of reference growth data, which limited comparability. There was a paucity of studies from Africa and the Arabian Peninsula, highlighting a large knowledge gap for low-resource settings. There was 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.

Conclusions: The monitoring of growth and nutritional status in children with SCD is an essential requirement for comprehensive care, facilitating early diagnosis of growth failure and nutritional intervention. Randomised controlled trials are necessary to assess the potential benefits of nutritional interventions in relation to growth, nutritional status and the pathophysiology of the disease.

Introduction

It is generally accepted that homozygous sickle cell disease (SS) impairs physical growth during childhood and early adolescence and that affected children are lighter and shorter than healthy counterparts. Growth retardation in sickle cell disease (SCD) is complex and multiple factors are likely to contribute, such as the haematological and cardiovascular state, social factors, endocrine function and metabolic and nutritional status.[1] Growth rate is inversely related to the degree of anaemia and is likely to be associated with deficiency of specific nutrients as well as low nutrient intake, decreased absorption and increased losses or utilisation.[2,3]

For example, the prevalence of underweight in American children with SCD was

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41% for moderate and 25% for severe under-nutrition[4] with a prevalence of wasting of 11%.[5] Stunting was reported in 44% of Ghanaian children and adolescents and almost all those with SS were underweight, irrespective of height.[6]

Although growth failure and under-nutrition are common, the underlying mechanisms have not been well studied and the precise role of intrinsic or extrinsic factors is unclear in relation to inadequate food intake or increased demands associated with higher energy expenditure and requirements. External and internal factors are likely to act together to a different degree against a variable genetic, environmental and socio-economic background. The aim of this review is to summarise the evidence related to poor growth and under-nutrition in children with SCD with regard to anthropometric status, disease severity, body composition and metabolism, micronutrient deficiency and endocrine dysfunction. An important aspect of these analyses is determining whether phenotype, nutritional deficits or anaemia individually contribute to growth restriction, or whether it is a combination of these factors which is important.

Methods

A literature search using the Medline/PUBMED, SCOPUS, SciELO and LILACS electronic databases for studies published up to July 2007 was conducted. The search terms sickle cell combined with nutrition, anthropometry, growth retardation, height and weight, body mass index (BMI) and specific micronutrients (zinc, iron, vitamins A, B group, C, D, E and folate) were used. Additional articles were identified by checking reference lists of retrieved articles. From a total of 423 published studies, 42 with relevant data (25 cross-sectional and 17 longitudinal) were selected. In addition, data were made available from unpublished studies (one cross-sectional and three longitudinal). The following data were extracted from these studies: age, disease severity, clinical presentation and growth parameters, use of blood transfusion, therapeutic interventions, micronutrient status and other nutritional and endocrine assessments, and haemoglobin genotype. The resulting data were tabulated by geographical location, age, anthropometric characteristics and types of controls.

There are four major genotypes within the definition of SCD: homozygous sickle cell (SS) disease, sickle haemoglobin C (SC) disease, sickle cell β^+ thalassaemia (S β^+ thalassaemia) and sickle cell β^0 thalassaemia (S β^0 thalassaemia).[7] The internationally accepted definition of SCD, two β-globin gene variants at least one of which is the sickle cell gene, is used and the gene variant for the four common genotypes are indicated when known. In this review, the term 'sickle cell anaemia' is used synonymously only for homozygous SS disease, and the majority of studies reviewed relate to this genotype.

Results

Nutritional status and disease severity

Inadequate intake can result from anorexia, a prominent symptom in affected children even in the absence of demonstrable infection, and it often precedes a painful crisis by days or weeks.[8] At the time of hospital admission, energy intake during acute illness is decreased by as much as 44% of the recommended daily amount (RDA) (SD 9%); during follow-up, intake is closer to 90% of RDA.[9] Dietary intakes can be reduced markedly prior to admission and remain sub-optimal for weeks.[10] In a Jamaican study, no significant relationship was demonstrated between haemoglobin concentration, reticulocyte count or irreversibly sickled cells and anthropometric measurements. Correlation with disease severity, measured by the number of

hospital admissions, showed no significant association with growth parameters, although a trend towards lower mean weight was found in patients who were admitted more often.[11] In pre-pubertal Jamaican children, levels of haemoglobin (Hb) and fetal haemoglobin (Hb F) decreased with an increasing number of hospitalisations of both sexes, although levels were positively associated with height and weight only in males.[12]

Vaso-occlusive crises and episodes of infection could increase energy expenditure.[13] A strong association between C-reactive protein and resting energy expenditure has been described, which might indicate a link between inflammation and a hyper-metabolic state in SCD.[14] Increased resting energy expenditure (REE) might relate to erythroid hyperactivity and accelerated red cell turnover owing to the short life span of sickled red blood cells. Low Hb levels and chronic anaemia are associated with hyperdynamic circulation and deterioration of cardiopulmonary function. This increases workload and, consequently, the demand for energy and nutrients.

There is evidence that nutrient supplementation can reduce clinical illness. Supplements given by the nasogastric route to SCD children with growth retardation (weight and height $<$5th centile) led to a rapid and sustained increase in growth and a reduction of pain crises and episodes of infection.[15] The authors found no lipid malabsorption and a normal histological appearance of the intestinal mucosa and submucosa and concluded that inadequate energy intake was responsible for the growth retardation.

Other therapeutic measures to reduce disease severity or complications (i.e. blood transfusion, splenectomy and hydroxyurea) might lead to improved nutritional status and growth. Children in the Stroke Prevention Trial in Sickle Cell Anaemia (STOP) who received transfusion regularly over a 2-year period demonstrated significant improvement in height, weight and BMI, with growth *Z*-scores approaching normal.[16] Those with homozygous SCD showed a significant reduction in whole body protein turnover (from 8.9 g/kg/d to 6 g/kg/d) after splenectomy, thereby contributing to positive energy balance[17] and acceleration in linear growth.[18] Therapy with hydroxyurea has been reported to decrease REE in treated SS children, suggesting that it might curtail a hypermetabolic state and offer clinically important secondary benefit.[19] In the Hydroxyurea Safety and Organ Toxicity (HUSOFT) extension study, improved growth rates were demonstrated in SS children treated with hydroxyurea. Their increased weight and height resulted in a growth pattern similar to that of children with Hb S β^+ thalassaemia or healthy controls.[20] Studies related to growth, specific micronutrients and disease severity are considered in later sections of this review.

Growth studies

Studies reporting growth of patients with SCD are summarised in Tables 1–6. Adult patients are often described as slender with low weight, relatively tall with long extremities, short trunk, narrow shoulders and hips, with a deep chest and increased anterior-posterior diameter. Many of these changes were found to be less pronounced and inconsistent in children, and some investigators considered this appearance in SCD to be an exaggeration of the normal characteristics of Africans.[21]Affected children were reported to have poor nutrition and their weight was consistently below the median reference values.

North American studies (Table 1). An early study of the growth of 48 American black children with sickle cell anaemia (aged 2–13 yrs) reported that the majority were thin with low weight and height. There was no correlation between growth parameters and the clinical course, arterial oxygen saturation or family childhood weight patterns.[22]

TABLE 1. *North American studies.*

Reference*	Year	Country	*n*	Design	Age (y)	Weight†	Height†	Other assessments	Controls	Comment
Whitten[22]	1961	USA	48	CS	2–13	96% <5th centile	81% <5th centile	Normal span & U/L segment	79 siblings Stuarts norms	No correlation with C/P or family weight pattern
Booker[25]	1964	USA	18	L	0–2	Around –2 SD	–	Deceleration began at age 6 m	Normal blacks *n*=86	Deficit coincides with start of infection and crises
Jimenez[23]	1966	USA	38	CS	8–17	Significantly lower mean	Significantly lower mean	Hypogonadism	Normal black children, *n*=89	Low U/L segment Span >height
McCormack[24]	1976	USA	46	CS	1–17	Significantly lower mean	Significantly lower mean	Low MUAC and calf circumference Bone age retarded	26 AS, standard of local black children, *n*=900	Delayed skeletal maturation in sickle cell trait (AS)
Kramer[26]	1980	Canada	14 10	L	0, 4, 5	Normal at birth, low subsequently	Normal at birth, low subsequently	Muscle mass area and HC not greatly affected	Black term newborn, *n*=71	Growth deficit started at 6 mths of age & increased over time
Luban[27]	1982	USA	55	L	13–18	Significantly below reference	Significantly below reference	Delayed sexual development Bone age retarded	NCHS reference	Hormonal assays normal in majority
Platt[28]	1984	USA	2115	CS	2–25	Significantly below reference	Significantly below reference	Sexual developmental delay	Howard University study of black children, *n*=2632	Growth deficit in SS >S β thalassaemia >SC, delayed menarche related to low weight
Phebus[29]	1984	USA	133	L	1–18	All <50th centile	All <50th centile	Maximum growth velocity after 14 y (F) & 16 y (M)	NCHS reference	Growth deficit by 2 yrs, M>F
Henderson[5]	1994	USA	63	CS	3–18	14% <5th centile	13% <5th centile	25% <5th centile 11% wasting (low wt/ht)	NCHS reference	Impaired growth & puberty in 11–18-yr-olds
Williams[98]	1997	USA	61	CS	2–17	22% <5th centile	19% <5th centile	Inadequate nutritional intake	NCHS reference	59% families below poverty line
Cepeda[30]	2000	USA	30	CS	8–19	Significantly low mean difference by average 12 kg	Significantly low mean difference by average 8 cm	Delayed sexual maturation by average 0.75 Tanner stage	Age, sex, race & socio–economic–matched, *n*=30	No significant difference in self–esteem or body image
Wang[16]	2005	USA	94	L	2–16	WAZ −0.71 score	HAZ −0.51 score	BMI −0.60 *Z*-score	NCHS reference Transfused 53 Standard care 41	Improved growth on long-term transfusion
Zemel[31]	2007	USA	148	L	0–18	26% <5th centile	22% <5th centile	BMI <5th centile in 24%, puberty delayed by 1–2 y	NCHS reference	Puberty affected by impaired growth & haematological status in F

* First author; CS, cross-sectional; L, longitudinal; F, female; M, male; C/P: clinical picture; HC, head circumference; MUAC, mid upper-arm circumference; BMI, body mass index; WAZ, weight-for-age *Z*-score; HAZ, height-for-age *Z*-score; † weight or height-for-age unless otherwise stated.

TABLE 2. *Jamaican studies.*

Reference*	Year	*n*	Design	Age (y)	Weight†	Height†	Other assessments	Controls	Comment
Ashcroft[35]	1972	99	CS	12–21	Mostly >–2SD	Variable	Bone age retarded >–2SD	Jamaican standard & local students, *n*=235	Younger cases shorter, older cases as tall as controls
Lowry[11]	1977	99	CS	2–13	Lower mean at all ages	No significant difference	Haematological parameters not correlated with deficit	Jamaican rural standard, *n*=2765	No correlation with hospital admission rate
Ashcroft[36]	1981	82	L	12–21	All below median	Below median	Menarche delayed by 2.3 y	Jamaican rural standard, *n*=12,934	Height exceeded standard by ages 16 (F) & 18 y (M)
Stevens[37]	1983	64	L	4–6	Significantly lower mean than controls	Significantly lower mean than controls	Low MUAC & short limbs	Normal AA, sex- & age-matched, *n*=123	Standing/sitting height normal
Stevens[32]	1986	455	L	0–9	Significantly lower mean than controls	Significantly lower mean than controls	Sexual & skeletal delay, SC not affected	Age- & sex-matched, *n*=231	Deficit began 2 y earlier in F than in M
Thomas[39]	2000	315	L	0–18	Normal at birth, low subsequently	Normal at birth, low subsequently	Growth catch-up at ages 15 (M) & 18 y (F)	NCHS reference	Growth reference curves produced from data

* First author; CS, cross-sectional; L, longitudinal; F, female; M, male; MUAC, mid upper-arm circumference; AA, normal adult haemoglobin; † weight or height-for-age unless otherwise stated.

TABLE 3. *Latin-American studies.*

Reference*	Year	Country	*n*	Design	Age	Weight†	Height†	Other assessments	Controls	Comment
Souza[40]	1983	Brazil	14	CS	6m–12y	All <10th centile	All <10th centile	Low serum zinc High serum cupper	NCHS reference	No correlation between zinc levels & growth deficit
Britto[42]	1985	Brazil	34	CS	6–20y	Significantly lower mean than controls	No significant difference	Menarche & bone age significantly lower than controls	AA *n*=16	Controls matched by age, race, economic status
Zago[43]	1992	Brazil	125	CS	7m–20y	40% <10th centile	31% <10th centile	Delayed sexual maturation	*n*=1041 & Brazilian standard	Post-pubertal weight deficit
Pellegrini-Braga[44]	1995	Brazil	34	L	0–18y	Significantly lower mean than controls	Significantly lower mean than controls	Growth velocity impairment, bone age delay, low serum zinc & ferritin	Siblings AS *n*=9 Non-siblings AA *n*=35	Growth deficit tends to increase with age. Hypercupraemia
Cipolotti[45]	2000	Brazil	76	CS	9m–20y	Median <50th centile	Median <50th centile	41% < expected parental height	NCHS reference	Father's height obtained from records
Silva[33]	2002	Brazil	100	L	5m–8y	WAZ –0.70 score	HAZ –0.65 score	Low BMI	NCHS reference	Growth deficit in SS >SC & M >F
Gonzáles-Fernández[46]	1992	Cuba	110	CS	4m–17y	No significant difference	No significant difference	No significant difference in bone age	Cuban standard	No significant differences in gestational age or birth weight

*First author; CS: cross-sectional; L: longitudinal; F: female; M: male; AA: normal adult haemoglobin; BMI: body mass index; WAZ: weight-for-age *Z*-score; HAZ: height-for-age *Z*-score; †weight or height for age unless otherwise stated.

TABLE 4. *African studies.*

Reference*	Year	Country	*n*	Design	Age (y)	Weight†	Height†	Other assessments	Controls	Comment
Mpemba-Loufoua[51]	2001	Congo	72	CS	10–18	Significantly lower mean than controls	Not measured	71% of cases no menarche at 14–18y, 10% in controls	AA females *n*=40	Only females included. Sexual maturity delayed in 37%
Mabiala-Babela[50]	2005	Congo	91	CS/L	8–14	Significantly lower mean than controls	Significantly lower mean than controls	Lower BMI, lean body mass, body fat %	AA *n*=95	Body composition decreased more in cases with severe disease
Thuilliez[52]	1996	Gabon	131	L	0–18	26.7% >–2SD	26.7% >–2SD	Pubertal delay in 13% Menarche mean age 15y	African multi-ethnic reference	Growth deficit increased with age
Ebomoyi[47]	1989	Nigeria	719	CS	2–13	All <50th centile	All <50th centile	MUAC <50th centile	Local controls *n*=979 & Harvard standard	SS growth less than controls & standards
Oyedeji[48]	1991	Nigeria	102	CS	9m–17y	All <3rd centile	Around 3rd centile of reference	Symptom frequency & education	Nigerian elites *n*=421	Low school performance & high school absence
Modebe[34]	1993	Nigeria	20	CS	17–35	Significantly lower mean in males	Significantly lower mean in males	Low BMI, MUAC & skin folds in males. Low daily energy intake in males, normal in females	Normal siblings of similar age *n*=15	Gender-related growth difference. Small sample for older group
Oredugba[49]	2002	Nigeria	177	CS	1–18	Around 3rd centile of reference	Around 3rd centile of reference	Low MUAC in 21% with maxillary protrusion & malocclusion.	Normal children *n*=122, local anthropometric reference	72% of cases & controls of low socio-economic status. No significant growth differences
Athale[53]	1994	Zambia	144	CS	10–38	60% <5th centile	53% <5th centile	Delayed sexual maturation. Educational delay & high school drop-out	NCHS reference	Children >10y included. Frequent psychosocial problems

*First author; CS, cross-sectional; L: longitudinal; F, female; M, male; AA, normal adult haemoglobin; MUAC, mid upper-arm circumference; BMI, body mass index; †weight or height for age unless otherwise stated.

TABLE 5. *The Middle East and India.*

Reference*	Year	Country	*n*	Design	Age (y)	Weight†	Height†	Other assessments	Controls	Comment
Soliman[54]	1999	Egypt	182	L	1–20	–	27% <−2 *Z*-score 67% <−1 *Z*-score	Low MUAC, U/L segments, delayed sexual maturation	Normal *n*=200. Constitutional GR *n*=30, GH defect *n*=25	Slow linear growth velocity increased with age, transfusion no effect
Mansour[55]	2003	Iraq	75	CS	18	77% <5th centile	47% <5th centile	BMI <20 in 77%, delayed sexual maturation	Males *n*=75 NCHS reference	All patients male, marked GR in severe disease
Jaiyesimi[56]	2002	Oman	97	CS	10m–12y	68% <5th centile 4% >50th centile	–	Moderate/severe disease in 71%	Age, sex-matched *n*=97 & NCHS reference	Compared with Jamaican reference 14% <3rd & 21% >50th centiles
Perrine[57]	1981	Saudi	21	L	0–3	No significant difference	No significant difference	No developmental delay	USA & Saudi references *n*=21	Mild disease with high Hb F levels
Al-Saqladi	2007	Yemen	102	CS	0.5–15	72% WAZ <−2 *Z*-score	55% HAZ <−2 *Z*-score	52% BMI <−2 *Z*-score. Low MAUC	NCHS reference	Author's unpublished data
Mukherjee[58]	2004	India	58	CS	2–14	Significantly lower mean than controls	Significantly lower mean than controls	Low BMI, MUAC, sitting height, skinfold thickness	Normal AA *n*=86	Arab–Indian haplotype with severe disease

*First author; CS, cross-sectional; L, longitudinal; F, female; M, male; HC, head circumference; MUAC, mid upper-arm circumference; BMI, body mass index; WAZ, weight-for-age *Z*-score; HAZ, height-for-age *Z*-score; GR, growth retardation; GH, growth hormone; AA, normal adult haemoglobin; † weight or height for age unless otherwise stated.

TABLE 6. *European studies.*

Reference*	Year	Country	*n*	Design	Age (y)	Weight†	Height†	Other assessments	Controls	Comment
Caruso-Nicoletti[59]	1992	Italy	76	CS	1–17	16% <3rd centile	80% <50th centile 10.5% <3rd centile	Benin haplotype in majority. Normal level somatomedin C	British reference (whites)	Moderate growth deficit. No difference between SS & βS thalassaemia
Dickerhoff	2007	Germany	341	L	2m–43y	12.6% <3rd centile	17.3% <3rd centile	–	German & Turkish references	Unpublished data
Fijnvandraat	2007	Netherlands	91	L	5–15	Weight/height 2.8% <−2 SD Age 5: 3% Age 10: 2% Age 15: 3%	25% <−2 SD Age 5: 10.6% Age 10: 14.3% Age 15: 50%	–	Dutch reference (whites)	Author's unpublished data
Mann[60]	1981	UK	96	L	3m–19y	–	11–16% <−2 SD	Varied clinical manifestations. Low mortality	British reference (whites)	Ethnic origin: West Indies, Africa, Yemen
Patey[61]	2002	UK	56	CS	3–9	Mean weight *Z*-score 0.32 Mean (AC) *Z*-score 0.93	Mean height *Z*-score 0.28 Mean (AC) *Z*-score 0.59	Mean BMI *Z*-score 0.23 similar to (CC) 0.30 but lower than (AC) 0.82	Caucasian $n=57$ African/Caribbean (AC) $n=63$	Significant difference compared with similar ethnic group
Telfer	2007	UK	180	L	2–15	6.5% <−2 *Z*-score Age 2: 3.7% Age 5: 3% Age 10: 8% Age 15: 11.5%	4.2% <−2 *Z*-score Age 2: 2% Age 5: 1.5% Age 10: 6.5% Age 15: 6.6%	4.2% <−2 *Z*-BMI score	Tanner reference	Unpublished data

*First author; CS: cross-sectional; L: longitudinal; F: female; M: male; HC: head circumference; BMI: body mass index; AC: African/Caribbean; CC: Caucasian; †weight or height for age unless otherwise stated.

Jimenez *et al.*[23] compared 20 SS females with 774 race-matched controls (11–40 yrs). There was delay in onset of menarche and age at first pregnancy, decreased fertility and an increased incidence of abortion and premature delivery. In a separate group of 38 cases in the same study, a low weight, height and upper-to-lower segments ratio was observed compared with 89 control black children of the same age. McCormack *et al.*[24] reported the growth of 46 American black children and adolescents with SS disease. In all age groups (1–17 yrs), they had lower mean height, weight, mid-upper-arm circumference (MUAC), thinner body build and delayed skeletal maturation compared with controls.

Height and weight deficit probably occurs early in life. Booker *et al.*[25] reported weight deceleration starting at about 4–6 months of age, coinciding with the onset of crises and infections and continuing during the 1st 2 years of life. Age-related growth deficit will be difficult to demonstrate accurately with longitudinal birth cohort studies until neonatal screening for haemoglobinopathies becomes more widely available. In a prospective study of 14 Canadian neonates with Hb SS, Kramer *et al.*[26] found no significant differences in birthweight or length compared with controls, indicating an absence of disease effect on fetal growth.[26] During follow-up of ten pairs of these children to 3–6 years of age, a growth deficit was noted from about 6 months of age.

In a 3-year longitudinal study which included 26 boys and 29 girls with sickle cell anaemia (13–18 yrs), there was subnormal weight and height and significant retardation in growth velocity. Skeletal maturation and sexual development were significantly retarded but, with adjustment for bone age and Tanner staging, sexual development was considered appropriate for bone age.[27]

A larger, cross-sectional, multi-centre study was undertaken which included 2115 cases with different sickle cell syndromes (1404 SS and the remainder with SC disease, S β^+ thalassaemia or S β^0 thalassaemia).[28] The mean height and weight of affected subjects were significantly below reference values and the difference became apparent after 7 years of age. Children with Hb SS and S β^0 thalassaemia were consistently smaller and less sexually mature than those with SC disease and S β^+ thalassaemia. Sexual maturation followed the pattern of height and weight, and time of menarche correlated well with weight and age.

Height and weight impairment at all ages and in both sexes compared with published growth reference values was reported in a cohort study of 133 SS American children followed from early childhood to adolescence.[29] The deficit in height and weight had commenced by 2 years, increased with age and was more pronounced in males of all ages. Growth velocity curves for 13 adolescents showed significant delay of pubertal growth. The mean difference in weight and height in a study of 30 SS children (8–19 yrs) paired with matched controls of the same age, sex, race and socio-economic status was a deficit of 12 kg weight and 8 cm height, with a 0.75-year delay in sexual maturation based on Tanner staging.[30] No difference in body image was detected between cases and controls. A recent longitudinal study of 148 SS children showed that the growth deficit for one or more indicators occurred in 84% of subjects, and 26%, 22% and 24% were <5th reference centile for weight, height and BMI, respectively. Puberty was delayed by 1–2 years. Disease severity assessed by hospitalisation, blood transfusion and haematological status was associated with longitudinal growth in females but not in males.[31] The cause for this sex difference is unclear, but other studies have reported similar findings and related it to differences in the level of Hb, Hb F, energy intake and hormonal changes, especially at the time of puberty.[12,29,32–34]

Jamaican studies (Table 2). Ashcroft *et al.*[35] studied growth in 99 adolescents (12–21

yrs) with sickle cell anaemia who had low mean weight and delayed skeletal age (based on hand radiography) compared with normal and sickle cell-trait (AS) controls. Height differences were variable: younger patients were shorter whereas older ones were as tall as controls.

Lowry *et al.*[11] studied 99 SS children (2–13 yrs) and reported a mean value for weight below Jamaican reference values for both sexes, although little difference was observed in height. In their follow-up study of 82 SS children (2–21 yrs), Ashcroft & Serjeant[36] reported that, while the weight deficit persisted, height continued to increase and final height was equal to or better than that of normal subjects. This was presumed to be a result of delayed epiphysial fusion with final height determined by the degree of delay. In a further study, the anthropometric measurements of 64 SS children showed a significant deficit in mean weight, height and MUAC by 4–6 years.[37] Limbs were shorter than those of controls, although the sitting–standing height ratio was normal.

A longitudinal study of children with SS and SC disease, followed from birth to 9 years of age and compared with normal AA controls, showed no birthweight differences for either gender; the weight deficit in the SS children commenced before the end of the 1st year of life.[32] The deficit appeared to be relatively more marked in girls and a similar trend was observed for height. Weight and height velocity deficits increased after the age of 7 years and there was a bone age difference by 5 years with a retardation of 0.4 years in boys and 0.6 years in girls. By the age of 8, this had increased to 1 and 1.3 years in boys and girls, respectively. Children with SC disease showed no growth deficit.[32] The time of the growth spurt was delayed by 1.4% years in 44 homozygous SCD adolescents and normal height was attained by 17.9 years.[38]

Disease-specific growth reference curves for children with homozygous SCD were produced using data obtained from a cohort of 315 children aged 0–18 years by the LMS (lambda-mu-sigma) method which is used to normalise and smooth growth centile curves.[39] Values from the LMS smoothed curves were used to generate centiles expressed at selected ages as standard deviation scores (*Z*-scores) using NCHS growth reference standards. Mean height and weight at birth in both sexes were similar to reference values but fell away subsequently before catching up at around 15 years in girls and 18 years in boys.[39] The applicability of this reference curve to countries other than Jamaica needs to be evaluated.

Latin-American studies (Table 3). In a study of 14 SCD Brazilian children (6 mths–12 yrs), all had growth retardation and weight and height were <10th centile of the NCHS reference.[40] Serum zinc levels were low but not correlated with growth deficit. Low serum zinc was also reported in 18 SS Venezuelan children.[41] In 34 Brazilian SCD patients (6–20 yrs), low weight-for-age but not height-for-age was significantly associated with delayed menarche and bone age.[42] Compared with pubertal matched controls, no difference in levels of serum-follicle stimulating hormone (FSH) or luteinising hormone (LH) before or after LH–FSH stimulation tests was detected. Another Brazilian study of 86 SS patients under 20 years of age reported weight and height <10th centile in 40% and 31% of cases, respectively, and the weight deficit persisted after puberty.[43] In a follow-up of 34 SS Brazilian patients (0–18 yrs), impaired growth velocity increased with age, and reduced weight and height were associated with low serum zinc and ferritin levels.[44] Family height channels were evaluated in 76 SCD children (9 mths–20 yrs) from Brazil and corrected for parental height. Overall, allowing for mid-parental height, 41% were below the expected centile value and did not attain normal height and weight in adulthood.[45] Although the maximum growth velocity occurred later than normal owing to delayed puberty, the magnitude of this spurt did not compensate

for the early growth delay and final size remained below normal. This contrasts with some Jamaican studies[36,38] and the difference might relate to genetic factors governing parental stature. In another group of 73 SS Brazilian children using NCHS reference values, comparison of *Z*-scores for height or weight-for-age and weight-for-height showed that almost 10% of cases were under-nourished (*Z*-score $\leqslant 2$).[33] After 1 year of follow-up, the weight- and height-for-age deficits became significant and were greater in boys. Conversely, Gonzáles *et al.*[46] reported no significant difference in weight, height and bone age in 110 SCD Cuban children less than 17 years of age (74 SS cases) compared with Cuban standards.

African studies (Table 4). Anthropometric values for weight, height and mid-arm circumference of 719 SS Nigerian children were reported to be <50th centile of the Harvard standards, the most marked deficit being weight-for-age.[47] Compared with healthy Nigerian children, 85 SS children (9 mths–17 yrs) showed weight and height below and around the 3rd centile.[48] In a study of 20 adults, anthropometric measurements were lower in males but not in females.[34] This was associated with lower daily energy and macronutrient intake by males than by controls. A further study of 177 Nigerian children and adolescents (1–18 yrs) with SCD reported anthropometric values close to the 3rd centile of reference values with no significant difference between cases and controls except at the age of 18 years.[49] A high prevalence (21%) of maxillary prognathism and malocclusion was reported among cases. However cases and controls were mostly from a lower socio-economic class, which might explain the lack of significant differences in anthropometric measurements between the groups. Evaluation of body composition in 91 Congolese SS children (8–14 yrs) showed significantly lower mean weight, height, BMI, lean body mass and percentage of body fat than in age-matched AA controls. Alteration in body composition correlated to the frequency of painful and anaemic crises.[50] Delayed sexual maturation was observed in 72 homozygous SCD Congolese girls with delay in the age at thelarche and menarche. Menarche had not occurred by 14–18 years in 71% of these cases compared with 10% of controls.[51] In a study from Gabon, 27% of 131 children with sickle cell anaemia (<18 yrs) had weights and heights <-2 SD compared with African multi-ethnic reference values.[52] In Zambian children with sickle cell anaemia, 60% and 53% were <5th centile for weight and height, respectively, compared with NCHS reference values.[53]

Middle East and India (Table 5). In a group of transfusion-dependent Egyptian children which included 110 cases of SCD, height was <-2 SD in 27%, and 51% showed a growth velocity <-1 SD. MUAC, triceps skinfold thickness and BMI were significantly lower than in controls, and linear growth was delayed increasingly with age.[54] Despite regular blood transfusion, onset of puberty and sexual maturation were delayed. Mean adult height was not attained in 96% of 75 SCD male Iraqi patients who were all 18 yrs of age, and 45% had delayed sexual maturation.[55] In 97 Omani children (90 SS, 7 S β^0 thalassaemia), weights in 68% were below the NCHS 5th centile compared with 28% of age- and sex-matched non-sicklers. When these data were plotted against Jamaican sickle cell reference values, 14% were <3rd centile.[56] Nutritional status in 102 SS Yemeni children (6 mths to 15 yrs) was compared with NCHS reference values. Growth deficit (<-2 *Z*-score) occurred in 72% based on weight-for-height, in 55% based on height-for-age and in 52% based on BMI (A.-W. M. Al-Saqladi, unpublished data). In Saudi Arabian children, there was no significant difference in serial height and weight measurements during the 1st 2 years of life in either 14 male or 7 female patients compared with matched controls from the eastern region of the country where the disease is generally mild.[57]

A study of 58 SS Indian children (2–14 yrs) reported significantly lower anthropometric values for all indicators except the upper/lower segment ratio compared with normal age- and sex-matched controls. Males and females were affected equally.[58]

European studies (Table 6). Moderate growth delay was reported in 76 white Sicilian children (1–17 yrs) with SCD.[59] Weight and height were <3rd centile of reference values for white British children in 16% and 10.5%, respectively. The majority had Benin haplotypes and showed no growth differences compared with β-S thalassaemia.

Mann[60] reported 61 SS patients (3 mths to 19 yrs) in England whose heights were >2 SD below the mean Caucasian reference value. The varied clinical manifestations compared with reports from Jamaica or North America led the author to conclude that variation depended on many factors including climate, endemic infection and the general standard of nutrition and medical care. Comparison of a further 56 SCD British children with controls of Caucasian (CC) or African/Caribbean (AC) origin showed that they were taller but that their weight and BMI were similar to CC controls.[61] Weight and BMI were significantly lower than in AC controls but there was no difference in height. Three unpublished longitudinal studies were identified, preliminary data for which are summarised in Table 6.

Summary. Growth retardation in children with SCD is well established and SS individuals are affected more severely than children with other sickle cell haemoglobinopathies. Growth failure occurs among affected children in all geographical areas, although the relevance and severity vary with location and are most marked in low-resource settings. Children with SCD have normal birthweight and length, with growth restriction commencing between 6 months and 2 years. European children show better growth than those elsewhere, probably indicating better nutrition and quality of care.

Body composition and energy metabolism

To understand the nutritional needs and interventions required in children with SCD, it is important to know the nature and magnitude of the body compositional deficits. A study of body composition in 36 Afro-American children with homozygous SCD found significantly lower *Z*-scores for weight, height, MUAC or upper arm fat and muscle in affected children.[62] A marked reduction in fat-free mass (FFM) and body fat indicated a global deficit of energy and protein stores, suggesting that nutritional needs were not being met.

Whole body protein turnover and resting metabolic rates are higher in SS adults than in AA controls. Protein turnover is an energy-consuming process which could account for increased energy expenditure. Patients with SCD disease could therefore be in a hyper-metabolic state, requiring higher energy and protein intake to maintain normal function.[63] The resting metabolic rate was found to be 19% higher in homozygous SCD than in AA controls and the difference was not related to the size of lean body mass.[64] When lean body mass or FFM are taken into account, REE per kg of FFM was 25–50% higher than normal.[65] The composition and tissue-specific metabolic rates comprising lean body mass/FFM in SS subjects is likely to differ from those of AA controls.[64,65] Whole body protein breakdown and synthesis was increased by 32% and 38%, respectively,[66] and the energy cost of increased protein synthesis was estimated to be approximately 50% of increased REE.[67] This increased energy expenditure and protein turnover could result from hyperactivity of bone marrow during erythroblastosis secondary to haemolysis and red cell destruction. The imbalance between energy requirements and expenditure would lead to a marginal nutritional state,

contributing to growth impairment that might potentially be corrected by energy supplements. To adapt to this state, there might be a reduction in physical activity. To compensate for their high resting metabolic rate, patients with SCD might try to economise on energy by decreasing physical activity. This mechanism cannot compensate for long-term energy deficiency or the imbalance between metabolic demands and energy consumption which ultimately lead to growth impairment.[68,69]

Pre-albumin, used to assess nutritional status, has been reported to be low in SCD.[70] Urinary loss of amino acids might also contribute to slow growth. One study reported no differences in the concentration of serum total proteins between SCD children and controls, but serum levels of pre-albumin, all essential and most non-essential amino acids were significantly lower with higher urinary concentration of amino acids.[71]

Changes in carbohydrate and lipid metabolism in SCD have been evaluated by measurement of whole body glucose and lipid metabolism in adults. Results showed that these were not significantly affected and the plasma concentration of insulin, glucagon, cortisol, nor-epinephrine and epinephrine were similar in patients and controls.[66] Serum levels of total phospholipids were within the normal range in children with sickle cell anaemia, while docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), total polyunsaturated fatty acids (PUFA)[72] and cholesterol[73,74] were decreased. With an imbalance between n-3 and n-6 long-chain PUFA in erythrocytes and plasma, alterations in the lipid layers of the red-cell wall might be antecedent to red-cell asymmetry, adhesion and aggregation and precede vaso-occlusion.[75]

Plasma concentration of type I procollagen carboxy-terminal propeptide (PICP), the major collagen produced by osteoblasts during bone formation, and urinary excretion of urinary pyridinoline cross-links (PYD) formed from type I collagen during bone resorption have been used as indirect measures of bone turnover. In adolescents with sickle cell anaemia compared with AA controls, these bone marrow resorption and formation markers were increased, suggesting increased protein formation and breakdown in bone marrow. This could relate to elevation in whole body protein turnover and REE in SS patients.[76] Bone mineral density, assessed by dual-energy X-ray in 25 children and adolescents (9–19 yrs) with severe sickle cell anaemia, was found to be reduced in 64%. This was associated with deficient calcium intake and low serum levels of vitamin D.[77]

Glutamine is the most abundant amino acid in humans and is the preferred fuel for rapidly dividing cells such as reticulocytes. Its use in children with sickle cell anaemia was reported to be 47% higher than in controls and to be associated with a 19% increase in REE and a 66% increase in cardiac output. These changes might be attributable to increased haemoglobin synthesis and cardiac workload.[78] Attempts to lower REE using oral glutamine led to a reduction of about 6%, which was greater in children who were underweight. Improved BMI and body fat components indicated that lowering REE by increasing energy intake and glutamine administration could be an effective way of promoting growth in children and adolescents with SCD.[79]

Metabolic studies suggest that children with SCD have a higher resting metabolic rate and REE, which increases their metabolic demands and requirements for protein and energy. Factors which contribute to higher REE include increases in protein turnover, erythropoieses, cardiac workload and underlying inflammation. The child's body composition, nutritional status and clinical condition all influence metabolic rate and nutritional requirements and these need to be well defined in order to understand the potential role of nutritional interventions for improving health.

Endocrine dysfunction and growth retardation

In children with SCD, delayed sexual maturation is frequently associated with growth retardation.[31] Although its contribution to growth deficit is unclear, it might not have a primary endocrine cause.[3] Determination of gonadotropin concentrations in 40 children with sickle cell anaemia (5–16 yrs) showed a significant increase in LH in children aged 5–10 years and normal levels in older children. The levels of LH and FSH were higher in patients than in controls at the same stage of development of secondary sexual characteristics. This suggested a variation in the rate of maturation of the hypothalamic–pituitary gonadotropin axis rather than gonadal hypofunction.[80]

Evaluation of gonadal function in adults with SCD showed that serum testosterone, dihydrotestosterone (DHT) and androstenedione levels were low.[81] High LH and FSH levels were observed before and after stimulation with gonadotropin-releasing hormone, which correlated with testicular size and retarded secondary sexual characteristics. This suggests that gonadal hypofunction is not related to pituitary failure but is consistent with primary gonadal failure. This study also reported reduced erythrocyte and hair zinc concentrations which significantly correlated with androgen status. The influence of chronic zinc deficiency on gonadal growth and function was considered important. Evaluation of the hypothalamic–pituitary axis by administration of gonadotropin-releasing hormone–thyrotropin-releasing hormones has demonstrated higher concentrations of LH, FSH, thyroid stimulatuig hormone and prolactin hormones in male patients than in controls, which suggests a primary gonadal failure in adults[82] and in children with extreme retardation of puberty.[83]

There is also some evidence for partial hypothalamic hypogonadism.[84] Significantly reduced concentrations of testosterone, LH and FSH in adults with SS disease supports gonadal hypofunction secondary to hypopituitarism.[85] Delayed testicular development has been demonstrated in male sicklers, predominantly in boys aged 10–15 years who had delayed puberty but attained normal sexual maturation.[43]

In a longitudinal study of 55 American children with SCD and reduced weight, height and retarded bone age, there was delayed sexual maturation which, though prolonged, progressed in an orderly manner.[27] The average age of menarche in affected girls was 15.4 *vs* 12.6 years in normal girls. In the majority of these children, hormonal assays indicated an intact pituitary–hypothalamic axis with appropriate adrenal and gonadal responses and only patients with marked delay in sexual maturation showed lower gonadal hormones. Age at menarche in Jamaican girls was delayed by 2.4 years in 99 cases with homozygous SS disease, and by 0.5 years in 69 SC cases compared with a mean age of 13 years in AA controls.[86] Weight was found to be the dominant determining factor for age at menarche in cases and controls. The authors considered their findings favoured sub-optimal nutrition as a cause of pubertal delay rather than an endocrine component.[86]

In 80 Saudi patients with sickle cell anaemia, hormonal assay showed normal levels of T3, T4 and growth hormone, low levels of cortisol, testosterone and LH, and variable changes in FSH.[87] These abnormalities occurred more frequently in the patients with severe disease. Studies of thyroid function have shown that blood levels of thyroxine, thyroxine-binding capacity and the free thyroxine index were not significantly different in 90 SS children (1–15 yrs) than in AS and AA controls.[88] Interest in growth hormone dysfunction has motivated a series of studies by Soliman and co-workers who demonstrated abnormalities in the growth hormone (GH)/insulin-like growth factor-I (IGF-I) axis.[54,89–92] In a study of 21 pre-pubertal SS children with poor growth (height $<$10th centile), defective GH secretion and low insulin-like

IGF-1 and IGF binding-protein-3 were demonstrated in 43%, with a reduced response of IGF-1 production to GH injection. The disease severity score was significantly higher in the group with defective GH secretion than in the group with normal GH secretion. The authors presumed there was partial resistance to GH and that these were major causes of slow growth, especially in individuals with severe SCD.[80] Although reduced elements of the GH/IGF-1 axis in SS children have been found, growth velocity shows poor correlation with endocrine assessment of the axis or thyroid function.[93] Other investigators have reported a significant correlation between IGF-1 and height velocity in a sub-group of sicklers with height <25th centile.[94] In an analysis of different β globulin haplotypes, the CAR/CAR haplotype has shown significantly lower mean growth velocity and reduced concentration of IGF-1 compared with BEN/BEN haplotype, leading to the conclusion that delay of growth in SCD was linked to intrinsic factors and disease severity.[93] In a small study of five SCD children with GH deficiency who received GH therapy for ⩾3 years, height *Z*-scores improved significantly.[95]

The normal pituitary response to stimulation tests and the conflicting results of hormonal assessment make it difficult to evaluate the role of endocrinal dysfunction in the pathogenesis of growth impairment. Endocrine function is altered in some children with SCD, and hormonal therapy such as GH or IGF-1 might offer therapeutic options.

Micronutrient deficiency

Micronutrient deficiency could be an important contributor to growth impairment in SCD. In an American study of 170 children (aged 2–12 years) with SCD, 22% were <5th centile in height and/or weight,[96] and the serum levels of zinc, retinol, pre-albumin and retinol binding protein were significantly lower in the 40 cases (who were either growth-retarded or normal) than in controls. Despite an adequate dietary intake of energy, protein, zinc and vitamin A, these children with SCD were leaner and lighter with lower red blood-cell zinc and serum vitamin A concentrations, and higher resting energy expenditure than controls.[97] These findings were reflected in a survey of 61 American SS patients and their families on nutrition knowledge and practice. Overall, 90% of participants were familiar with the different food groups but most failed to consume an appropriate amount of different food groups, and 59% had incomes below the poverty level. The authors concluded that inadequate intake of nutrients was contributing to poor child growth in lower socioeconomic families.[98] A recent study evaluated dietary intake by 24-hour recall over four annual visits in 97 American children with homozygous SCD and reported a suboptimal intake of many nutrients across all ages, including vitamins D and E, folate, calcium, magnesium and zinc, with a trend towards poor diet with increasing age, particularly during adolescence.[99]

Folic acid was the first micronutrient deficiency to be associated with SCD and has been reported frequently.[100–103] Folate deficiency and megaloblastic erythropoiesis were observed in about 10% of patients in Nigeria, and therapeutic administration of folic acid resulted in improved height and weight as well as correction of haematological changes.[104] Other investigators have failed to demonstrate a correlation between growth retardation and folate deficiency as folate supplementation produced no change in haematological or growth parameters.[105–108] Routine supplementation in SCD has been questioned, particularly in developed countries where folate requirements could be provided by a fortified food intake.[109] Vitamin B_6 (pyridoxine) deficiency in adults with SCD has also been reported.[110] In children, assessment of vitamin B_6 status by determination of serum concentrations of pyridoxal 5-phosphate

(PLP) (the major co-enzyme of vitamin B_6) showed that 77% were below the reference cut-off, and there were significant positive associations between PLP levels and BMI *Z*-scores, weight and MUAC.[111] Reduced levels of other B vitamins including B_{12}[112] and riboflavin[113] have been reported. Folic acid and vitamins B_6 and B_{12} are important co-factors in metabolism of the sulphur-containing amino acid homocysteine, and deficiencies can lead to hyperhomocysteinaemia. In the general population, raised homocysteine concentrations are linked to increased risk of cardiovascular disease and stroke.[114] Plasma homocysteine is reported to be elevated in adults[115] and children[116,117] with SCD and significantly so when complicated by stroke.[118] Homocysteine levels can be lowered by supplementation with folic acid or vitamins B_6 and B_{12}. In addition to the maintenance of effective erythropoiesis, these micronutrients can prevent tissue accumulation of homocysteine, thus reducing the risk of endothelial damage and thrombosis.[119–121]

Serum vitamin A status was reported as marginal in 66% of American children with SCD and deficient in 17%. BMI *Z*-scores were low, and there were higher rates of hospital admission of vitamin A-deficient patients than of those with normal levels.[122]

Zinc deficiency in SCD occurs at levels suggesting chronic zinc depletion and appears to be associated with chronic haemolysis and hyperzincuria.[123] Growth retardation and hypogonadism were observed in zinc-depleted men, suggesting its contribution to impaired growth and sexual maturation in SCD.[81,124] In 104 American children (0.4–18 yrs), low plasma zinc was reported in 44% of SS cases and, compared with SS cases with normal plasma zinc, was associated with impairment of height, weight, FFM, skeletal growth and sexual and skeletal maturation.[125] Supplements of elemental zinc (10 mg/day) given for 12 months to 20 children with SCD led to improved rates of linear growth but there was no effect on BMI.[126]

Iron deficiency might not be associated with SCD owing to the availability of iron from red cell destruction and increased intestinal iron absorption in response to chronic anaemia.[127] Even so, patients receiving sporadic transfusions do not acquire excessive iron burden during the 1st 2 decades of life.[128] Iron deficiency in SCD is common,[129] particularly among children living in developing countries where iron deficiency anaemia is highly prevalent.[130] Depletion of iron storage diagnosed by bone marrow examination was reported in a high proportion of SCD children (36–50%) in India and Nigeria.[131–133] Iron deficiency was reported in 16% of non-transfused American children diagnosed by their response to iron therapy.[134] This contrasted with a study of 104 non-transfused patients who showed no haematological or biochemical evidence of iron deficiency.[135] A study of Jamaican children followed from birth to 5 years reported low serum iron in patients and controls by 1 year of age, but levels subsequently became normal.[136] However, a recent cross-sectional study of 141 Jamaican SCD children (1–5 yrs) which used several measurements to determine iron status showed that 8.5% of cases were iron-deficient.[137] Although the exact mechanism of iron deficiency in SCD is not clear, the most probable cause is excessive urinary loss secondary to chronic haemolysis.[138]

Iron deficiency in SCD might be beneficial and possibly ameliorate sickling by decreasing MCHC, which reduces haemolysis, thus prolonging red-cell lifespan[139,140] and reducing painful crises[141] (which can be precipitated by iron therapy).[142] Evidence for the clinical benefits of iron deficiency is minimal and is limited because of difficulties in assessing disease severity.[143] Iron deficiency is associated with growth and intellectual impairment[144] and, in a growing child with SCD, iron requirements are increased. Iron-deficient children are at risk of both growth and neurocognitive impairment imposed by the disease and

compounded by iron deficiency. These consequences should be considered before iron supplementation is withheld.

Vitamin E deficiency occurs in SCD,[145] with a high prevalence in children in developing countries.[146,147] Vitamin E has anti-oxidant properties that could protect red cells against oxidative stress and its administration leads to a decrease in the percentage of irreversibly sickled cells, which might alleviate symptoms.[148] Deficiency of vitamins C[149] and D[150] and of minerals such as magnesium[151] and selenium[152] has been reported, although the exact pathophysiological consequences and contribution to growth delay in SCD are unclear. The potential benefits of individual nutrient or multi-micronutrient supplementation remain to be established.

Food substances with anti-oxidant activity, which might protect red cell membranes from oxidative injury, have been used to treat SCD.[153,154] In a small pilot study, oral administration of dietary omega-3 fatty acid, provided as menhaden fish oil containing docosahexanoic acid and eicosapentanoic acid, produced significant reduction in the mean number of painful crises, blood coagulability and platelet adhesion molecule expression.[155] Omega-3 fatty acids are important components of red cell membranes and their blood levels have been correlated with indices of disease severity and haemoglobin concentration in steady-state SCD. This suggests that there are clinical benefits through protection against haemolysis and reduction in vaso-occlusive episodes or ischaemic organ damage.[156] L-arginine is the natural amino acid substrate for the synthesis of nitric oxide, a potent vasodilator that is deficient during sickle cell crises. When administered orally at a dose of 0.1 g/kg three times a day, it led to a significant reduction in pulmonary artery systolic pressure in SCD patients with pulmonary hypertension.[157] This is consistent with vaso-constriction being a significant contributor to vaso-occlusion.[158] Oral supplementation of magnesium pidolate (540 mg/kg/d) has been used to elevate erythrocyte magnesium and prevent potassium loss by inhibition of the K-Cl co-transport system, resulting in improved sickle red-cell hydration and a decrease in the median number of painful days during a 6-month period of magnesium therapy.[159]

Several micronutrient deficiencies have been reported in patients with SCD. Folic acid is widely administered, usually daily, to children with SCD, although the optimal dose is unclear, which relates to uncertainty concerning the daily requirement. Other nutrients such as zinc, glutamine, l-arginine and anti-oxidants might have therapeutic benefits, and their clinical efficacy needs to be determined.

Future Perspectives

Under-nutrition relates to increased morbidity and mortality in all children, and contributes to poor clinical outcome and severity of disease in children with SCD. Despite major advances in understanding the molecular and genetic basis for SCD, there has been little progress towards lessening the obvious nutritional problems faced by these children.[160] There has been limited evaluation of a variety of nutritional interventions that could influence the natural history of SCD.[161] Improving the nutritional status and growth of these children could have a favourable impact on their clinical course and prognosis. Evaluation of a comprehensive clinical care programme in a sub-Saharan Africa setting produced encouraging results and showed that improved growth and reduced disease severity can be attained.[162] There are good opportunities for such programmes with the introduction of neonatal screening, the identification of children with SCD at birth and early interventions using essential health packages.

Growth monitoring with appropriate nutritional support as part of the comprehensive care of children with SCD should be

promoted. If the types of nutritional deficiency are known, then clear nutritional advice and care can be given by health workers to children and their families. This allows the identification of children who do not adhere to nutritional interventions and of high-risk cases. It might facilitate the use of alternative interventions including drugs, hormones or other treatments in specific cases.

Small stature and delayed sexual maturity can carry long-term psychological consequences that affect the ability of the adolescent with SCD to form normal relationships with the opposite sex, leading to low self-esteem and depression.[163] Growth retardation has been associated with impaired mental development and a low intelligence quotient,[164] and nutritional interventions with their potential for improving long-term growth and development could improve prognosis, particularly if commenced in early childhood before growth retardation becomes established. These interventions might lead to reduction in the severity of crises and vascular complications, or episodes of vasoconstriction.

There is little information on the influence of several important genetic polymorphisms on nutritional status in SCD. For example, methylene-tetrahydrofolate reductase deficiency, which is not infrequent in subjects with SCD,[165–168] would influence host folate status and homocysteine metabolism with possible effects on sickle cell vasculopathy. Similarly, glucose-6-phosphate dehydrogenase deficiency could affect severity of haemolysis in sickle cell anaemia, although some studies of this genotype have shown little additive effect.[169] Pooled data from studies of different haplotype profiles need to be interpreted carefully, taking these various factors into consideration.

In order to assess the benefits for child growth and the reduction of disease severity, randomised trials of nutritional interventions in infancy and early childhood combined with appropriate health care packages are required. There are few studies from Africa and the Arabian Peninsula and increased efforts are required to address this disparity, particularly in low-resource settings.

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References

1 Serjeant GR. *Sickle Cell Disease*, 2nd edn. Oxford: Oxford University Press, 1992.
2 Enwonwu CO. Nutritional support in sickle cell anaemia: theoretical considerations. *J Natl Med Assoc* 1988; **80**:139–44.
3 Wethers DL. Delayed growth and sexual maturation in sickle cell disease. *Ann N Y Acad Sci* 1989; **565**:137–42.
4 Warrier RP, Kuvibidila S, Gordon L, Humbert J. Transport proteins and acute phase reactant proteins in children with sickle cell anaemia. *J Natl Med Assoc* 1994; **86**:33–9.
5 Henderson RA, Saavedra JM, Dover GJ. Prevalence of impaired growth in children with homozygous sickle cell anaemia. *Am J Med Sci* 1994; **307**:405–7.
6 Konotey-Ahulu F. The sickle cell disease patient: natural history from a clinico-epidemiological study of the first 1550 patients of Korle Bu Hospital Sickle Cell Clinic. Watford, UK: Tetteh-A'Domeno, 1996.
7 Serjeant GR. The clinical features of sickle cell disease. *Baillières Clin Haematol* 1993; **6**:93–115.
8 Scott RB, Ferguson AD, Jenkins ME, Clark HM. Studies in sickle-cell anaemia. VIII. Further observations on the clinical manifestations of sickle-cell anaemia in children. *Am J Dis Child* 1955; **90**:682–91.
9 Malinauskas BM, Gropper SS, Kawchak DA, Zemel BS, Ohene-Frempong K, Stallings VA. Impact of acute illness on nutritional status of infants and young children with sickle cell disease. *J Am Diet Assoc* 2000; **100**:330–4.
10 Fung EB, Malinauskas BM, Kawchak DA, *et al.* Energy expenditure and intake in children with sickle cell disease during acute illness. *Clin Nutr* 2001; **20**:131–8.

11 Lowry MF, Desai P, Ashcroft MT, Serjeant BF, Serjeant GR. Heights and weights of Jamaican children with homozygous sickle cell disease. *Hum Biol* 1977; **49**:429–36.

12 Singhal A, Morris J, Thomas P, Dover G, Higgs D, Serjeant G. Factors affecting prepubertal growth in homozygous sickle cell disease. *Arch Dis Child* 1996; **74**:502–6.

13 Singhal A, Doherty JF, Raynes JG, *et al*. Is there an acute-phase response in steady-state sickle cell disease? *Lancet* 1993; **341**:651–3.

14 Hibbert JM, Hsu LL, Bhathena SJ, *et al*. Proinflammatory cytokines and the hypermetabolism of children with sickle cell disease. *Exp Biol Med (Maywood)* 2005; **230**:68–74.

15 Heyman MB, Vichinsky E, Katz R, *et al*. Growth retardation in sickle-cell disease treated by nutritional support. *Lancet* 1985; **1**:903–6.

16 Wang WC, Morales KH, Scher CD, *et al*. Effect of long-term transfusion on growth in children with sickle cell anaemia: results of the STOP trial. *J Pediatr* 2005; **147**:244–7.

17 Badaloo A, Emond A, Venugopal S, Serjeant G, Jackson AA. The effect of splenectomy on whole body protein turnover in homozygous sickle cell disease. *Acta Paediatr Scand* 1991; **80**:103–5.

18 Singhal A, Thomas P, Kearney T, Venugopal S, Serjeant G. Acceleration in linear growth after splenectomy for hypersplenism in homozygous sickle cell disease. *Arch Dis Child* 1995; **72**:227–9.

19 Fung EB, Barden EM, Kawchak DA, Zemel BS, Ohene-Frempong K, Stallings VA. Effect of hydroxyurea therapy on resting energy expenditure in children with sickle cell disease. *J Pediatr Hematol Oncol* 2001; **23**:604–8.

20 Hankins JS, Ware RE, Rogers ZR, *et al*. Long-term hydroxyurea therapy for infants with sickle cell anaemia: the HUSOFT extension study. *Blood* 2005; **106**:2269–75.

21 Winsor T, Burch G. Habitus of patients with active sickle cell anaemia of long duration. *Arch Intern Med* 1945; **76**:47–53.

22 Whitten CF. Growth status of children with sickle-cell anaemia. *Am J Dis Child* 1961; **102**:355–64.

23 Jimenez CT, Scott RB, Henry LW, Sampson CC, Ferguson AD. Studies in sickle cell anaemia. XXVI. The effects of homozygous sickle cell disease on the onset of menarche, pregnancy, fertility, pubescent changes, and body growth in Negro subjects. *Am J Dis Child* 1966; **111**:497–504.

24 McCormack MK, Dicker L, Katz SH, *et al*. Growth patterns of children with sickle-cell disease. *Hum Biol* 1976; **48**:429–37.

25 Booker CR, Scott RB, Ferguson AD. Studies in sickle cell anaemia. Xxii. Clinical manifestations of sickle cell anaemia during the first two years of life. *Clin Pediatr (Phila)* 1964; **3**:111–15.

26 Kramer MS, Rooks Y, Washington LA, Pearson HA. Pre- and postnatal growth and development in sickle cell anaemia. *J Pediatr* 1980; **96**:857–60.

27 Luban NL, Leikin SL, August GA. Growth and development in sickle cell anaemia. Preliminary report. *Am J Pediatr Hematol Oncol* 1982; **4**:61–5.

28 Platt OS, Rosenstock W, Espeland MA. Influence of sickle hemoglobinopathies on growth and development. *N Engl J Med* 1984; **311**:7–12.

29 Phebus CK, Gloninger MF, Maciak BJ. Growth patterns by age and sex in children with sickle cell disease. *J Pediatr* 1984; **105**:28–33.

30 Cepeda ML, Allen FH, Cepeda NJ, Yang YM. Physical growth, sexual maturation, body image and sickle cell disease. *J Natl Med Assoc* 2000; **92**:10–14.

31 Zemel BS, Kawchak DA, Ohene-Frempong K, Schall JI, Stallings VA. Effects of delayed pubertal development, nutritional status, and disease severity on longitudinal patterns of growth failure in children with sickle cell disease. *Pediatr Res* 2007; **61**:607–13.

32 Stevens MC, Maude GH, Cupidore L, Jackson H, Hayes RJ, Serjeant GR. Prepubertal growth and skeletal maturation in children with sickle cell disease. *Pediatrics* 1986; **78**:124–32.

33 Silva CM, Viana MB. Growth deficits in children with sickle cell disease. *Arch Med Res* 2002; **33**:308–12.

34 Modebe O, Ifenu SA. Growth retardation in homozygous sickle cell disease: role of calorie intake and possible gender-related differences. *Am J Hematol* 1993; **44**:149–54.

35 Ashcroft MT, Serjeant GR, Desai P. Heights, weights, and skeletal age of Jamaican adolescents with sickle cell anaemia. *Arch Dis Child* 1972; **47**:519–24.

36 Ashcroft MT, Serjeant GR. Growth, morbidity, and mortality in a cohort of Jamaican adolescents with homozygous sickle cell disease. *West Indian Med J* 1981; **30**:197–201.

37 Stevens MC, Hayes RJ, Serjeant GR. Body shape in young children with homozygous sickle cell disease. *Pediatrics* 1983; **71**:610–14.

38 Singhal A, Thomas P, Cook R, Wierenga K, Serjeant G. Delayed adolescent growth in homozygous sickle cell disease. *Arch Dis Child* 1994; **71**:404–8.

39 Thomas PW, Singhal A, Hemmings-Kelly M, Serjeant GR. Height and weight reference curves for homozygous sickle cell disease. *Arch Dis Child* 2000; **82**:204–8.

40 Souza NM, Tone LG, Collares EF, Souza IM. Valores séricos de zinco em crianças com hemoglobinopatia (anaemia falciforme, beta talassemia e S-talassemia/serum zinc levels in children with homoglobinopathy (sickle cell

anaemia, beta-talassemia and S-talassemia). *J Pediatr (Rio J)* 1983; **55**:385–8.
41 Figuera L, Carneiro L, Villarroel J. Anaemia drepanocítica y niveles sericos de zinc/ Drepanocitic anaemia and zinc seric tenels. *Arch Venez Pueric Pediatr* 1994; **57**:182–5.
42 Britto MMS, Alves AFP, Rabelo MM. Alterações no desenvolvimento somático e sexual na anaemia falciforme (SS) e traço falcêmico (AS) [Changes of the somatic and sexual development in sickle cell anaemia (SS) and sickling trace (AS)]. *Arq Bras Endocrinol Metab* 1985; **29**:111–14.
43 Zago MA, Kerbauy J, Souza HM, *et al*. Growth and sexual maturation of Brazilian patients with sickle cell diseases. *Trop Geogr Med* 1992; **44**:317–21.
44 Pellegrini-Braga J, Kerbauy J, Fisberg M. Zinc, copper and iron and their interrelations in the growth of sickle cell patients (Zinc, cobre, hierro y su interrelación con el crescimiento de niños con anaemia falciforme). *Arch Latinoam Nutr* 1995; **45**:198–203.
45 Cipolotti R, Caskey MF, Franco RP, *et al*. Childhood and adolescent growth of patients with sickle cell disease in Aracaju, Sergipe, north-east Brazil. *Ann Trop Paediatr* 2000; **20**:109–13.
46 Gonzáles-Fernándes P, Svarch E, Garriga E. Crecimiento y desarrollo en las hemoglobinopatias S (Growth and development in hemoglobinopathy-S). *Rev Cuba Hematol Inmunol Hemoter* 1992; **8**:12–22.
47 Ebomoyi E, Adedoyin MA, Ogunlesi FO. A comparative study of the growth status of children with and without SS disease at Ilorin, Kwara State, Nigeria. *Afr J Med Med Sci* 1989; **18**:69–74.
48 Oyedeji GA. The health, growth and educational performance of sickle cell disease children. *East Afr Med J* 1991; **68**:181–9.
49 Oredugba FA, Savage KO. Anthropometric finding in Nigerian children with sickle cell disease. *Pediatr Dent* 2002; **24**:321–5.
50 Mabiala-Babela JR, Massamba A, Tsiba JB, Moulongo JG, Nzingoula S, Senga P. Body composition in Negro African children suffering from sickle cell disease. A mixed cross-sectional longitudinal study in Brazzaville, Congo. *Bull Soc Pathol Exot* 2005; **98**:394–9.
51 M'Pemba-Loufoua AB, Nzingoula S, Moubouh-Akouala F, Oba A. Pubertal development in girls with homozygote sickle cell disease. A propos of 72 cases. *Bull Soc Pathol Exot* 2001; **94**:326–9.
52 Thuilliez V, Ditsambou V, Mba JR, Mba Meyo S, Kitengue J. Current aspects of sickle cell disease in children in Gabon. *Arch Pediatr* 1996; **3**:668–74.
53 Athale UH, Chintu C. The effect of sickle cell anaemia on adolescents and their growth and development—lessons from the sickle cell anaemia clinic. *J Trop Pediatr* 1994; **40**:246–52.
54 Soliman AT, el Zalabany M, Amer M, Ansari BM. Growth and pubertal development in transfusion-dependent children and adolescents with thalassemia major and sickle cell disease: a comparative study. *J Trop Pediatr* 1999; **45**:23–30.
55 Mansour AA. Influence of sickle hemoglobinopathy on growth and development of young adult males in Southern Iraq. *Saudi Med J* 2003; **24**:544–6.
56 Jaiyesimi F, Pandey R, Bux D, Sreekrishna Y, Zaki F, Krishnamoorthy N. Sickle cell morbidity profile in Omani children. *Ann Trop Paediatr* 2002; **22**:45–52.
57 Perrine RP, John P, Pembrey M, Perrine S. Sickle cell disease in Saudi Arabs in early childhood. *Arch Dis Child* 1981; **56**:187–92.
58 Mukherjee MB, Gangakhedkar RR. Physical growth of children with sickle cell disease. *Indian J Hum Genet* 2004; **10**:70–2.
59 Caruso-Nicoletti M, Mancuso M, Spadaro G, Samperi P, Consalvo C, Schiliro G. Growth and development in white patients with sickle cell diseases. *Am J Pediatr Hematol Oncol* 1992; **14**:285–8.
60 Mann JR. Sickle cell haemoglobinopathies in England. *Arch Dis Child* 1981; **56**:676–83.
61 Patey RA, Sylvester KP, Rafferty GF, Dick M, Greenough A. The importance of using ethnically appropriate reference ranges for growth assessment in sickle cell disease. *Arch Dis Child* 2002; **87**:352–3.
62 Barden EM, Kawchak DA, Ohene-Frempong K, Stallings VA, Zemel BS. Body composition in children with sickle cell disease. *Am J Clin Nutr* 2002; **76**:218–25.
63 Badaloo A, Jackson AA, Jahoor F. Whole body protein turnover and resting metabolic rate in homozygous sickle cell disease. *Clin Sci (Lond)* 1989; **77**:93–7.
64 Singhal A, Davies P, Sahota A, Thomas PW, Serjeant GR. Resting metabolic rate in homozygous sickle cell disease. *Am J Clin Nutr* 1993; **57**:32–4.
65 Kopp-Hoolihan LE, van Loan MD, Mentzer WC, Heyman MB. Elevated resting energy expenditure in adolescents with sickle cell anaemia. *J Am Diet Assoc* 1999; **99**:195–9.
66 Borel MJ, Buchowski MS, Turner EA, Peeler BB, Goldstein RE, Flakoll PJ. Alterations in basal nutrient metabolism increase resting energy expenditure in sickle cell disease. *Am J Physiol* 1998; **274**:e357–64.
67 Borel MJ, Buchowski MS, Turner EA, Goldstein RE, Flakoll PJ. Protein turnover and energy expenditure increase during exogenous nutrient availability in sickle cell disease. *Am J Clin Nutr* 1998; **68**:607–14.

68 Singhal A, Davies P, Wierenga KJ, Thomas P, Serjeant G. Is there an energy deficiency in homozygous sickle cell disease? *Am J Clin Nutr* 1997; **66**:386–90.

69 Barden EM, Zemel BS, Kawchak DA, Goran MI, Ohene-Frempong K, Stallings VA. Total and resting energy expenditure in children with sickle cell disease. *J Pediatr* 2000; **136**:73–9.

70 Jain SK, Ross JD, Duett J, Herbst JJ. Low plasma prealbumin and carotenoid levels in sickle cell disease patients. *Am J Med Sci* 1990; **299**:13–15.

71 Van der Jagt DJ, Kanellis GJ, Isichei C, Patuszyn A, Glew RH. Serum and urinary amino acid levels in sickle cell disease. *J Trop Pediatr* 1997; **43**:220–5.

72 Enomoto TM, Isichei C, Van der Jagt DJ, Fry DE, Glew RH. Decreased polyunsaturated fatty acids in sickle cell anaemia. *J Trop Pediatr* 1998; **44**:28–34.

73 el-Hazmi MA, Warsy AS, Al-Swailem A, Al-Swailem A, Bahakim H. Red cell genetic disorders and plasma lipids. *J Trop Pediatr* 1995; **41**:202–5.

74 Van der Jagt DJ, Shores J, Okorodudu A, Okolo SN, Glew RH. Hypocholesterolemia in Nigerian children with sickle cell disease. *J Trop Pediatr* 2002; **48**:156–61.

75 Ren H, Obike I, Okpala I, Ghebremeskel K, Ugochukwu C, Crawford M. Steady-state haemoglobin level in sickle cell anaemia increases with an increase in erythrocyte membrane n-3 fatty acids. *Prostaglandins Leukot Essent Fatty Acids* 2005; **72**:415–21.

76 Buchowski MS, de la Fuente FA, Flakoll PJ, Chen KY, Turner EA. Increased bone turnover is associated with protein and energy metabolism in adolescents with sickle cell anaemia. *Am J Physiol Endocrinol Metab* 2001; **280**:e518–27.

77 Lal A, Fung EB, Pakbaz Z, Hackney-Stephens E, Vichinsky EP. Bone mineral density in children with sickle cell anaemia. *Pediatr Blood Cancer* 2006; **47**:901–6.

78 Salman EK, Haymond MW, Bayne E, *et al.* Protein and energy metabolism in prepubertal children with sickle cell anaemia. *Pediatr Res* 1996; **40**:34–40.

79 Williams R, Olivi S, Li CS, *et al.* Oral glutamine supplementation decreases resting energy expenditure in children and adolescents with sickle cell anaemia. *J Pediatr Hematol Oncol* 2004; **26**:619–25.

80 Olambiwonnu NO, Penny R, Frasier SD. Sexual maturation in subjects with sickle cell anaemia: studies of serum gonadotropin concentration, height, weight, and skeletal age. *J Pediatr* 1975; **87**:459–64.

81 Abbasi AA, Prasad AS, Ortega J, Congco E, Oberleas D. Gonadal function abnormalities in sickle cell anaemia. Studies in adult male patients. *Ann Intern Med* 1976; **85**:601–5.

82 Parshad O, Stevens MC, Preece MA, Thomas PW, Serjeant GR. The mechanism of low testosterone levels in homozygous sickle-cell disease. *West Indian Med J* 1994; **43**:12–14.

83 Singhal A, Gabay L, Serjeant GR. Testosterone deficiency and extreme retardation of puberty in homozygous sickle-cell disease. *West Indian Med J* 1995; **44**:20–3.

84 Landefeld CS, Schambelan M, Kaplan SL, Embury SH. Clomiphene-responsive hypogonadism in sickle cell anaemia. *Ann Intern Med* 1983; **99**:480–3.

85 Dada OA, Nduka EU. Endocrine function and haemoglobinopathies: relation between the sickle cell gene and circulating plasma levels of testosterone, luteinising hormone (LH) and follicle stimulating hormone (FSH) in adult males. *Clin Chim Acta* 1980; **105**:269–73.

86 Serjeant GR, Singhal A, Hambleton IR. Sickle cell disease and age at menarche in Jamaican girls: observations from a cohort study. *Arch Dis Child* 2001; **85**:375–8.

87 El-Hazmi MA, Bahakim HM, Al-Fawaz I. Endocrine functions in sickle cell anaemia patients. *J Trop Pediatr* 1991; **38**:307–13.

88 Lukanmbi FA, Adeyokunnu AA, Osifo BO, Bolodeoku JO, Dada OA. Endocrine function and haemoglobinopathies: biochemical assessment of thyroid function in children with sickle-cell disease. *Afr J Med Med Sci* 1986; **15**:25–8.

89 Soliman AT, Darwish A, Asfour MG. Empty sella in short children with and without hypothalamic-pituitary abnormalities. *Indian J Pediatr* 1995; **62**:597–603.

90 Soliman AT, Darwish A, Mohammed SH, Bassiony MR, El-Banna N, Asfour M. Circulating growth hormone (GH), insulin-like growth factor-I (IGF-I) and free thyroxine, GH response to clonidine provocation and CT scanning of the hypothalamic-pituitary area in children with sickle cell disease. *J Trop Pediatr* 1995; **41**:285–9.

91 Soliman AT, El-Banna N, Al-Salmi I, De Silva V, Craig A, Asfour M. Growth hormone secretion and circulating insulin-like growth factor-I (IGF-I) and IGF binding protein-3 concentrations in children with sickle cell disease. *Metabolism* 1997; **46**:1241–5.

92 Soliman AT, Bererhi H, Darwish A, Al-Zalabani MM, Wali Y, Ansari B. Decreased bone mineral density in prepubertal children with sickle cell disease: correlation with growth parameters, degree of siderosis and secretion of growth factors. *J Trop Pediatr* 1998; **44**:194–8.

93 Luporini SM, Bendit I, Manhani R, Bracco OL, Manzella L, Giannella-Neto D. Growth hormone

and insulin-like growth factor I axis and growth of children with different sickle cell anaemia haplotypes. *J Pediatr Hematol Oncol* 2001; **23**:357–63.
94 Collett-Solberg PF, Fleenor D, Schultz WH, Ware RE. Short stature in children with sickle cell anaemia correlates with alterations in the IGF-I axis. *J Pediatr Endocrinol Metab* 2007; **20**:211–18.
95 Nunlee-Bland G, Rana SR, Houston-Yu PE, Odonkor W. Growth hormone deficiency in patients with sickle cell disease and growth failure. *J Pediatr Endocrinol Metab* 2004; **17**:601–6.
96 Finan AC, Elmer MA, Sasanow SR, McKinney S, Russell MO, Gill FM. Nutritional factors and growth in children with sickle cell disease. *Am J Dis Child* 1988; **142**:237–40.
97 Gray NT, Bartlett JM, Kolasa KM, Marcuard SP, Holbrook CT, Horner RD. Nutritional status and dietary intake of children with sickle cell anaemia. *Am J Pediatr Hematol Oncol* 1992; **14**:57–61.
98 Williams R, George EO, Wang W. Nutrition assessment in children with sickle cell disease. *J Assoc Acad Minor Phys* 1997; **8**:44–8.
99 Kawchak DA, Schall JI, Zemel BS, Ohene-Frempong K, Stallings VA. Adequacy of dietary intake declines with age in children with sickle cell disease. *J Am Diet Assoc* 2007; **107**:843–8.
100 Jonsson U, Roath OS, Kirkpatrick CI. Nutritional megaloblastic anaemia associated with sickle cell states. *Blood* 1959; **14**:535–47.
101 MacIver JE, Went LN. Sickle-cell anaemia complicated by megaloblastic anaemia of infancy. *Br Med J* 1960; **1**:775–9.
102 Alperin JB. Folic acid deficiency complicating sickle cell anaemia. A study on the response to titrated doses of folic acid. *Arch Intern Med* 1967; **120**:298–306.
103 Lopez R, Shimizu N, Cooperman JM. Recurrent folic acid deficiency in sickle cell disease. *Am J Dis Child* 1973; **125**:544–8.
104 Watson-Williams EJ. Folic acid deficiency in sickle-cell anaemia. *East Afr Med J* 1962; **39**:213–21.
105 Pearson HA, Cobb WT. Folic acid studies in sickle-cell anaemia. *J Lab Clin Med* 1964; **64**:913–21.
106 Liu YK. Folate deficiency in children with sickle cell anaemia. *Am J Dis Child* 1974; **127**:389–93.
107 Rabb LM, Grandison Y, Mason K, Hayes RJ, Serjeant B, Serjeant GR. A trial of folate supplementation in children with homozygous sickle cell disease. *Br J Haematol* 1983; **54**:589–94.
108 Serjeant GR. Treatment of sickle cell disease in early childhood in Jamaica. *Am J Pediatr Hematol Oncol* 1985; 7:235–9.
109 Wang WC. Role of nutritional supplement in sickle cell disease. *J Pediatr Hematol Oncol* 1999; **21**:176–8.
110 Natta CL, Reynolds RD. Apparent vitamin B_6 deficiency in sickle cell anaemia. *Am J Clin Nutr* 1984; **40**:235–9.
111 Nelson MC, Zemel BS, Kawchak DA, *et al.* Vitamin B_6 status of children with sickle cell disease. *J Pediatr Hematol Oncol* 2002; **24**:463–9.
112 Al-Momen AK. Diminished vitamin B_{12} levels in patients with severe sickle cell disease. *J Intern Med* 1995; **237**:551–5.
113 Ajayi OA, George BO, Ipadeola T. Clinical trial of riboflavin in sickle cell disease. *East Afr Med J* 1993; **70**:418–21.
114 Clarke R. Homocysteine-lowering trials for prevention of heart disease and stroke. *Semin Vasc Med* 2005; **5**:215–22.
115 Lowenthal EA, Mayo MS, Cornwell PE, Thornley-Brown D. Homocysteine elevation in sickle cell disease. *J Am Coll Nutr* 2000; **19**:608–12.
116 Balasa VV, Kalinyak KA, Bean JA, Stroop D, Gruppo RA. Hyperhomocysteinemia is associated with low plasma pyridoxine levels in children with sickle cell disease. *J Pediatr Hematol Oncol* 2002; **24**:374–9.
117 Marian TK. *Folic Acid and Homocysteine Levels in Children with Sickle Cell Disease in The Gambia*. Liverpool School of Tropical Medicine, UK: Master of Tropical Paediatrics thesis, 2001.
118 Houston PE, Rana S, Sekhsaria S, Perlin E, Kim KS, Castro OL. Homocysteine in sickle cell disease: relationship to stroke. *Am J Med* 1997; **103**:192–6.
119 Ballas SK, Saidi P. Thrombosis, megaloblastic anaemia, and sickle cell disease: a unified hypothesis. *Br J Haematol* 1997; **96**:879–80.
120 van der Dijs FP, Fokkema MR, Dijck-Brouwer DA, *et al.* Optimization of folic acid, vitamin B(12), and vitamin B(6) supplements in pediatric patients with sickle cell disease. *Am J Hematol* 2002; **69**:239–46.
121 Sulaimon AS. *Homocysteine Levels in Children with Sickle Cell Disease Following Vitamin B_{12} Supplmentation*. Liverpool School of Tropical Medicine, UK: Master of Tropical Paediatrics thesis, 2002.
122 Schall JI, Zemel BS, Kawchak DA, Ohene-Frempong K, Stallings VA. Vitamin A status, hospitalizations, and other outcomes in young children with sickle cell disease. *J Pediatr* 2004; **145**:99–106.
123 Prasad AS, Schoomaker EB, Ortega J. Zinc deficiency in sickle cell disease. *Clin Chem* 1975; **21**:582–7.
124 Prasad AS, Ortega J, Brewer GJ, Oberleas D, Schoomaker EB. Trace elements in sickle cell disease. *JAMA* 1976; **235**:2396–8.
125 Leonard MB, Zemel BS, Kawchak DA, Ohene-Frempong K, Stallings VA. Plasma zinc status,

growth, and maturation in children with sickle cell disease. *J Pediatr* 1998; **132**:467–71.
126 Zemel BS, Kawchak DA, Fung EB, Ohene-Frempong K, Stallings VA. Effect of zinc supplementation on growth and body composition in children with sickle cell disease. *Am J Clin Nutr* 2002; **75**:300–7.
127 Erlandson ME, Schulman I, Smith CH. Studies on congenital hemolytic syndromes. III. Rates of destruction and production of erythrocytes in sickle cell anaemia. *Pediatrics* 1960; **25**:629–44.
128 O'Brien RT. Iron burden in sickle cell anaemia. *J Pediatr* 1978; **92**:579–82.
129 Davies S, Henthorn J, Brozovic M. Iron deficiency in sickle cell anaemia. *J Clin Pathol* 1983; **36**:1012–15.
130 Jeyakumar LH, Akpanyung EO, Akinyemi AA, Emerole GO. An investigation into the iron status of children with sickle-cell disease in western Nigeria. *J Trop Pediatr* 1987; **33**:326–8.
131 Nagaraj Rao J, Sur AM. Iron deficiency in sickle cell disease. *Acta Paediatr Scand* 1980; **69**:337–40.
132 Okeahialam TC, Obi GO. Iron deficiency in sickle cell anaemia in Nigerian children. *Ann Trop Paediatr* 1982; **2**:89–92.
133 Oluboyede OA, Ajayi OA, Adeyokunnu AA. Iron studies in patients with sickle cell disease. *Afr J Med Med Sci* 1981; **10**:1–7.
134 Vichinsky E, Kleman K, Embury S, Lubin B. The diagnosis of iron deficiency anaemia in sickle cell disease. *Blood* 1981; **58**:963–8.
135 Stettler N, Zemel BS, Kawchak DA, Ohene-Frempong K, Stallings VA. Iron status of children with sickle cell disease. *J Parenter Enteral Nutr* 2001; **25**:36–8.
136 Serjeant GR, Grandison Y, Mason K, Serjeant B, Sewell A, Vaidya S. Haematological indices in normal negro children: a Jamaican cohort from birth to five years. *Clin Lab Haematol* 1980; **2**:169–78.
137 King L, Reid M, Forrester TE. Iron deficiency anaemia in Jamaican children, aged 1–5 years, with sickle cell disease. *West Indian Med J* 2005; **54**:292–6.
138 Washington R, Boggs DR. Urinary iron in patients with sickle cell anaemia. *J Lab Clin Med* 1975; **86**:17–23.
139 Lincoln TL, Aroesty J, Morrison P. Iron-deficiency anaemia and sickle-cell disease: a hypothesis. *Lancet* 1973; **2**:260–1.
140 Castro O, Poillon WN, Finke H, Massac E. Improvement of sickle cell anaemia by iron-limited erythropoiesis. *Am J Hematol* 1994; **47**:74–81.
141 Bouchair N, Manigne P, Kanfer A, *et al.* Prevention of sickle cell crises with multiple phlebotomies. *Arch Pediatr* 2000; **7**:249–55.
142 Haddy TB, Castro O. Overt iron deficiency in sickle cell disease. *Arch Intern Med* 1982; **142**:1621–4.
143 Koduri PR. Iron in sickle cell disease: a review why less is better. *Am J Hematol* 2003; **73**:59–63.
144 Oski FA. Iron deficiency in infancy and childhood. *N Engl J Med* 1993; **329**:190–3.
145 Sindel LJ, Baliga BS, Bendich A, Mankad V. Nutritional deficiencies associated with vitamin E deficiency in sickle cell patients; the effect of vitamin supplementation. *Nutr Res* 1990; **10**:267–73.
146 Ndombi IO, Kinoti SN. Serum vitamin E and the sickling status in children with sickle cell anaemia. *East Afr Med J* 1990; **67**:720–5.
147 Shukla P, Graham SM, Borgstein A, Nhlane A, Harper G, Brabin BJ. Sickle cell disease and vitamin E deficiency in children in developing countries. *Trans R Soc Trop Med Hyg* 2000; **94**:109.
148 Natta CL, Machlin LJ, Brin M. A decrease in irreversibly sickled erythrocytes in sickle cell anaemia patients given vitamin E. *Am J Clin Nutr* 1980; **33**:968–71.
149 Westerman MP, Zhang Y, McConnell JP, *et al.* Ascorbate levels in red blood cells and urine in patients with sickle cell anaemia. *Am J Hematol* 2000; **65**:174–5.
150 Buison AM, Kawchak DA, Schall J, Ohene-Frempong K, Stallings VA, Zemel BS. Low vitamin D status in children with sickle cell disease. *J Pediatr* 2004; **145**:622–7.
151 Zehtabchi S, Sinert R, Rinnert S, *et al.* Serum ionized magnesium levels and ionized calcium-to-magnesium ratios in adult patients with sickle cell anaemia. *Am J Hematol* 2004; **77**:215–22.
152 Natta CL, Chen LC, Chow CK. Selenium and glutathione peroxidase levels in sickle cell anaemia. *Acta Haematol* 1990; **83**:130–2.
153 Ohnishi ST, Ohnishi T, Ogunmola GB. Sickle cell anaemia: a potential nutritional approach for a molecular disease. *Nutrition* 2000; **16**:330–8.
154 Takasu J, Uykimpang R, Sunga MA, Amagase H, Niihara Y. Aged garlic extract is a potential therapy for sickle-cell anaemia. *J Nutr* 2006; **136**:803–5S.
155 Tomer A, Kasey S, Connor WE, Clark S, Harker LA, Eckman JR. Reduction of pain episodes and prothrombotic activity in sickle cell disease by dietary n-3 fatty acids. *Thromb Haemost* 2001; **85**:966–74.
156 Okpala IE. New therapies for sickle cell disease. *Hematol Oncol Clin North Am* 2005; **19**:975–87, ix.
157 Morris CR, Morris SM Jr, Hagar W, *et al.* Arginine therapy: a new treatment for pulmonary hypertension in sickle cell disease? *Am J Respir Crit Care Med* 2003; **168**:63–9.

158 Stuart MJ, Nagel RL. Sickle-cell disease. *Lancet* 2004; **364**:1343–60.
159 De Franceschi L, Bachir D, Galacteros F, *et al.* Oral magnesium pidolate: effects of long-term administration in patients with sickle cell disease. *Br J Haematol* 2000; **108**:284–9.
160 Prasad AS. Malnutrition in sickle cell disease patients. *Am J Clin Nutr* 1997; **66**:423–4.
161 Reed JD, Redding-Lallinger R, Orringer EP. Nutrition and sickle cell disease. *Am J Hematol* 1987; **24**:441–55.
162 Rahimy MC, Gangbo A, Ahouignan G, *et al.* Effect of a comprehensive clinical care program on disease course in severely ill children with sickle cell anaemia in a sub-Saharan African setting. *Blood* 2003; **102**:834–8.
163 Mankad VN. Growth and development in sickle hemoglobinopathies. *Am J Pediatr Hematol Oncol* 1992; **14**:283–4.
164 Knight S, Singhal A, Thomas P, Serjeant G. Factors associated with lowered intelligence in homozygous sickle cell disease. *Arch Dis Child* 1995; **73**:316–20.
165 Zimmerman SA, Ware RE. Inherited DNA mutations contributing to thrombotic complications in patients with sickle cell disease. *Am J Hematol* 1998; **59**:267–72.
166 Kutlar A, Kutlar F, Turker I, Tural C. The methylene tetrahydrofolate reductase (C677T) mutation as a potential risk factor for avascular necrosis in sickle cell disease. *Hemoglobin* 2001; **25**:213–17.
167 Fawaz NA, Bashawery L, Al-Sheikh I, Qatari A, Al-Othman SS, Almawi WY. Factor V-Leiden, prothrombin G20210A, and MTHFR C677T mutations among patients with sickle cell disease in Eastern Saudi Arabia. *Am J Hematol* 2004; **76**:307–9.
168 Couto FD, Boas WV, Lyra I, *et al.* A C677T methylenetetrahydrofolate reductase (MTHFR) polymorphism and G20210A mutation in the prothrombin gene of sickle cell anaemia patients from Northeast Brazil. *Hemoglobin* 2004; **28**:237–41.
169 Nagel RL, Steinberg MH. Role of epistatic (modifier) genes in the modulation of the phenotypic diversity of sickle cell anaemia. *Pediatr Pathol Mol Med* 2001; **20**:123–36.