Int Health 2017; **9**: 327–334
doi:10.1093/inthealth/ihx035 Advance Access publication 28 September 2017

Comparative study of the growth and nutritional status of Brazilian and Nigerian school-aged children with sickle cell disease

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Received 13 January 2017; revised 4 May 2017; editorial decision 11 August 2017; accepted 31 August 2017

Background: Comparative studies of patients in different sociogeographic/ecological zones may unravel potential environmental and nutritional factors influencing disease phenotype. In sickle cell disease (SCD), differential access to comprehensive care may influence their growth and nutritional status.

Methods: From June 2015 to February 2016, steady-state nutritional parameters of 109 Brazilian and 95 Nigerian children with SCD attending routine clinic visits at Universidade Federal de São Paulo, Brazil and Obafemi Awolowo University Teaching Hospital, Ile-Ife (Ilesa unit), respectively, were compared.

Results: A relatively high proportion of the children in both centres (23.5%) were wasted [body-mass index (BMI)-for-age *z*-score<−2). BMI-for-age *z*-score, height-for-age *z*-score, upper arm fat area and fat percentage were lower in the Nigerian cohorts. More Nigerians, 29.5% (28/95) against 18.3% (20/109) were wasted, and had short stature, [12.6% (12/95) vs. 3.7% (4/109)] than Brazilians. A higher proportion of Brazilian patients were overweight or obese (9.2 vs. 4.3%), and taller for age (15.6 vs. 8.4%). None of the Nigerian patients had severe vitamin D deficiency, only 12.6% (12/95) had suboptimal vitamin D and 1.1% (1/95) had low serum zinc levels, unlike 79.8% (87/109) of the Brazilian patients with suboptimal vitamin D and 10.1% (11/109) with low zinc.

Conclusion: Undernutrition is still prevalent among the two cohorts. Nigerian patients were thinner and had reduced linear growth for age. This observation justifies the continued need for specialized nutritional care for children with SCD. In addition to hydroxyurea therapy, research is needed to determine appropriate nutritional intervention and exercise regimens for these children.

Keywords: Brazilian, Children, Growth, Nigerian, Nutritional status, Sickle cell disease

Introduction

SCD is the most common haematological hereditary disease in Brazil and Nigeria.[1,2] It is estimated that about 4% (2–8%) of the world population carry an abnormal haemoglobin gene, with sickle cell anaemia (SCA) being the most common form of haemoglobinopathy.[3] Approximately 20–25 million people live with SCA worldwide, out of which about 12–15 million reside in sub-Saharan Africa, and annually about 300 000 children with the gene are born globally.[4] The disease affects people across the globe particularly sub-Saharan Africa, India, Mediterranean and Southern European countries.[5] Ancient and recent population migrations have also carried the disease to the Caribbean, South and North America, and Northern Europe.[5]

Reduced growth and delayed development are common in children with SCD to the extent that some researchers are advocating the use of modified growth charts when monitoring their nutritional state.[6] Usually, these patients experience a progressive decrease in growth velocity up to adolescence. In addition, they have a delay in bone maturation, epiphysis fusion during puberty and sexual development.[5] Micronutrients, such as serum zinc, 25-hydroxyvitamin D (25-OHD), selenium and retinol, are suboptimal in SCD due to reduced appetite and poor dietary intake, increased energy and metabolic requirements, and reduced physical activity.[7,8] SCD-directed therapies, such as hydroxyurea (HU) and chronic blood transfusion have been

associated with significant reduction in the overall morbidity and mortality.[9,10] These therapies could possibly improve growth and nutritional status of children with SCD. While many Brazilian children with SCD are being treated with hydroxyurea, the majority of Nigerian children with the disease do not have access to this drug. Apart from differences in the haplotypes of SCD between Brazilian and Nigerian patients, important modifiable factors such as nutritional status of patients may influence SCD severity and, hence, its associated morbidity and mortality.[11,12] The predominant SCD haplotype among Brazilian patients is the Central African Republic, *CAR* (Bantu) haplotype, while Benin (*BEN*) haplotype is the leading haplotype among Nigerian patients.[11,12] The *CAR* haplotype is usually associated with a lower level of foetal haemoglobin and, subsequently, more severe phenotype compared with the *BEN* haplotype.

Although, in low income countries, children with SCD frequently experience poor growth and impaired nutritional state, few reports from some high income nations show that these children are now becoming overweight and obese.[6,13] Recent studies have also shown that obesity-related complications, such as systemic hypertension, obstructive sleep apnoea, avascular osteonecrosis and asthma, are on the increase in children and adolescents with SCD.[6,13] These comorbidities are associated with increased SCD-related mortality.

The SCD phenotype is very variable, and many genetic and environmental modulating factors have been identified. Comparative studies of patients in different sociogeographic and ecological zones afford an opportunity to investigate potential environmental and other factors that influence the phenotype. This study aimed at comparing differences in nutritional status as measured by anthropometric and biochemical variables (serum zinc and 25-OHD) between two cohorts of children with SCD followed in Ilesa, Southwest, Nigeria, and São Paulo, Brazil.

Methods

This is a descriptive cross-sectional study in which demographic, clinical, nutritional and laboratory data of paediatric patients with SCD in steady state were collected.

Study location

The study was carried out at the paediatric haematology clinics of the Escola Paulista de Medicina, Universidade Federal de São Paulo (UNIFESP), Brazil and Obafemi Awolowo University Teaching Hospital (OAUTH), Ilesa Unit, Nigeria. Nigeria, the largest country in West Africa with an estimated population of about 170 million people, is located on latitude 10°N of equator and longitude 8°E of Greenwich Meridian. It has an abundance sunlight throughout the year. The Nigerian study participants are predominantly Yoruba, of Ife-Ijesa extraction, in the south-western part of the country. Ilesa, the study centre is an urban city and is located about 250 km north-east of Lagos, the former Nigerian capital. A typical Yoruba diet is high in carbohydrate. The paediatric haematology clinic of OAUTH runs weekly and sees an average of 25 patients/week. A total of about 400 children with SCD are registered in the clinic. The clinic offers daily chemoprophylaxis, such as folate and preventive antimalaria treatment (proguanil). Hydroxyurea is prescribed only when indicated and the patient's family can afford the cost. Although oral penicillin prophylaxis is not currently routinely prescribed, all children are offered Pneumococcal and Haemophilus influenza type B vaccination.

Brazil, the largest country in South America is located on latitude 10°S and longitude 55°W of Equator. São Paulo city, like other cities in south-east Brazil, experiences a prolonged annual period of cold weather and reduced exposure to sunlight. The population is heterogenous comprising diverse ethnic groups, including native Latin Americans, African, Asian, Arabs, Jewish, North American and Europeans, particularly Italians. The paediatric haematology clinic of UNIFESP also runs every week. The clinic offers comprehensive SCD care, including hydroxyurea and chronic blood transfusion therapy, transcranial Doppler ultrasonography for stroke prevention, and daily folate chemoprophylaxis, oral penicillin, Pneumococcal and Haemophilus influenza type B vaccination are also routinely given.

Patients

The study included 109 Brazilian and 95 Nigerian children aged 4–11 years who had been diagnosed with SCA. They routinely attend the paediatric haematology clinics of the respective hospitals. All the study participants were in steady state at the time of recruitment, i.e. they had been free of crisis (painful or anaemic), infections or any other acute illness for at least four consecutive weeks, and had not been transfused 3 months prior to the study.[14] All the eligible children that attended the clinics during the study period (June 2015 to February 2016) were recruited consecutively. The age limits were set at 11 and 4 years as only few children among those younger than 4 years are managed with hydroxyurea and only very few among those older than 11 years are managed without hydroxyurea in Brazil. Children on a chronic blood transfusion programme, and those taking medications known to affect growth or nutritional status (e.g. growth hormone, glucocorticoid therapy) were not included in the study. Institutional approval was obtained from the Ethics and Research Committees of the hospitals independently before commencement of the study. Also, written informed consent was obtained from each study participant.

Data on the sociodemographics (age, sex and socioeconomic status) were obtained from each patient through a pretested questionnaire. Socioeconomic status of the parents was determined using the occupation of the father and the highest academic qualification of the mother.[15,16] Clinical history and physical findings, including splenic and liver enlargement were obtained through a pretested questionnaire and by review of relevant medical charts. Lifetime SCD complications were as defined by Ballas *et al.*[14] In addition, the frequencies of vaso-occlusive episodes, hospitalization and transfusion that occurred in the previous 12 months were recorded. Acute significant painful episode was defined as a painful event requiring a hospital visit, and the use of oral and/or parenteral analgesics.

Growth status

Weight was measured to the nearest 0.1 kg on a scaletronix digital electronic scale (Scaletronix, White Plains, NY) and height

to the nearest 0.1 cm with a stadiometer (Holtain, Crymych, UK). From the weight and height, BMI was calculated as weight (kg)/height^2 (m^2). Weight and height were transformed into *z*-scores for height/age, weight/age and weight/height, and BMI for age and sex, and then compared with the reference values using WHO/National Center for Health Statistics (NCHS) reference standards.[17] Height-for-age *z*-score<−2 was defined as stunting, BMI-for-age *z*-score <−2 (BMI-Z<−2) from the mean as wasting. Those with BMI-for-age *z*-score <−2, but >−3 were moderately wasted, and those with BMI-for-age *z*-score<−3 as severely wasted. Overweight was defined as BMI-for-age *z* score >2, but ≤+3 from the mean; and obese if BMI-for-age *z*-score was >3 from the mean. Normal weight was BMI-for-age *z*-score within the mean ±2

Nutritional assessment

The assessment of nutritional status was based on triceps skinfold (TSF) thickness, mid-upper arm circumference (MUAC), upper arm area (UAA), upper arm fat area (UAFA) and upper arm muscle area (UAMA). Measures of MUAC were combined with the TSF thickness to calculate UAA, UAFA and UAMA as shown in the following equations:

$$\text{UAMA (cm}^2\text{)} = (\text{MUAC} - \pi\text{TSF})^2/4\pi$$

$$\text{UAA (cm}^2\text{)} = \pi/4\,(\text{MUAC}/\pi)^2$$

$$\text{UAFA (cm}^2\text{)} = \text{UAA—UAMA and Fat\%} = \text{UAFA} \times 100/\text{UAA},$$

where π is 3.1416.[18]

MUAC was measured on a freely-hanging left upper arm midway between the acromion and the olecranon process using a flexible, but non-stretchable tape to the nearest 0.1 cm in all the subjects. TSF was measured using the Harpenden skinfold callipers. The skin was pinched between index finger and the thumb half-way down the back of the arm. This was then gently gripped by the callipers to measure the skin fold thickness in millimetres. The mean of two measurements was recorded.

Haematological parameters

Laboratory data such as haematocrit, white blood cell count and differential, mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), platelet count and HbF% were obtained. Complete blood counts and white blood cell count differentials were performed using auto-haemoanalyser Pentra 60, Horiba® (HORIBA ABX SAS, Belgium) machine in the Ile-Ife cohort and the Siemens ADVIA 2120 (Siemens AG, Erlangen, Germany) machine in the São Paulo cohort. The HbF% was measured using BIO-RAD® D10 (Bio-Rad Laboratories, Inc., Hercules, CA) high performance liquid chromatography (HPLC) in both centres.

Serum 25-hydroxyvitamin D and zinc level

Blood samples for serum 25-OHD and zinc were drawn between 8 a.m. and 11 a.m., and centrifuged within 1 hour of collection at 3000 rev/min for 15 minutes at room temperature to extract the plasma. The plasma was then divided into aliquots in plain screw cap specimen bottles and stored frozen at −20°C until analysed. Analysis of serum 25-OHD levels was done with HPLC in both centres using a standard protocol. Serum levels ≥30 ng/mL were considered sufficient, 20–29.9 ng/mL as insufficient, values <20 ng/mL as vitamin D deficiency and values <10 ng/mL as severe deficiency.[19] Analysis of serum zinc levels was done using atomic absorption spectrophotometry in both centres using a standard protocol. Zinc deficiency was defined as serum zinc <70 ng/ml, normal zinc level as 70–120 ng/ml and high zinc level as values >120 ng/ml.

Statistical analysis

Statistical tests were performed using SPSS version 17.0. Both parametric and non-parametric tests were used as appropriate, taking into account the variability and the nature of the distributions of the variables studied. Kolmogorov–Smirnov statistics was used to test the normality of the distribution. Continuous variables were compared according to site with independent sample *t*-test, Mann–Whitney test, analysis of variance or Kruskall–Wallis tests, and categorical variables with Pearson's χ^2 test or Fisher's exact test. The statistical significance level for the alpha error was p≤0.05 and 95% confidence interval exclusion of unity.

Results

Patient characteristics

A total of 204 children, comprising 109 Brazilian children and 95 Nigerian children with SCA were studied. Age and gender distribution were similar between the two cohorts (Table 1). None of the Nigerian patients was on hydroxyurea therapy compared with 67.0% (73/109) of the Brazilian patients. 33.0% (36/109) of Brazilian patients were not on hydroxyurea therapy. More of the Nigerian children experienced ≥3 significant pain episodes in the 12 months preceding the study than the Brazilian children, 31.6% (30/95) vs. 15.6% (17/109), p=0.007, 95% CI = 0.2–0.8. However, the rates of SCD-related admission and transfusion were significantly higher among Brazilian than Nigerian patients, 49.5% (54/109) vs. 31.6% (30/95), p=0.009, 95% CI = 1.2–3.8 and 35 (32.1%) vs. 14 (14.8%), p=0.004, 95% CI = 1.4–5.5, respectively.

Clinical complications

Higher proportions of patients from São Paulo compared with the Nigerian cohort had histories of ACS, 60.6% (66/109) vs. 29.5% (28/95), p<0.001; splenic sequestration 52.3% (57/109) vs. 3.2% (3/95), p<0.001 and cholelithiasis 31.2% (34/109) vs. 0% (0/95), p<0.001. Osteomyelitis was, however, more commonly diagnosed among Nigerian children with SCD, 16.8% (16/95) than the Brazilian children, 3.7% (4/109), p=0.023.

Nutritional status

BMI-for-age *z*-score, height-for-age *z*-score, UAFA and fat percentage were lower in the Nigerian cohort vs. the São Paulo cohort (Table 2). A higher proportion of patients from the Nigeria cohort were wasted, 28 (29.5%) vs. 20 (18.3%), and of short stature, 12 (12.6%) vs. 4 (3.7%) respectively, while more

Table 1. Comparison of sociodemographic and clinical parameters between SCD children from the Federal University of Sao Paulo Teaching Hospital, Sao Paulo, Brazil and Obafemi Awolowo University Teaching Hospital, Ilesa Unit, Nigeria

Parameters	Sao Paulo, Brazil		Ilesa, Nigeria n=95	p-value
	All patients=109	HU-naive=36		
Age (mean±SD) in years	7.4±2.3	7.1±2.2	7.4±2.5	NS
Age groups				
4–5 years	28 (25.7)	11 (30.6)	27 (28.4)	
6–7 years	30 (27.5)	11 (30.6)	22 (23.2)	NS
8–9 years	26 (23.9)	8 (22.2)	23 (24.2)	
10–11 years	25 (22.9)	6 (16.7)	23 (24.2)	
Gender (M/F), n (%)	51 (46.8)/58 (53.2)	17 (47.2)/19 (52.8)	53 (54.7)/43 (45.3)	NS
Socioeconomic class (I/II/III) in %	10.1/41.3/48.6	10.1/41.3/48.6	15.8/56.8/27.4	0.008*
Age at diagnosis				
Birth–1 month	93 (85.3)	26 (72.2)	0 (0)	
Infancy	13 (11.9)	9 (25.0)	17 (17.9)	<0.001
1–5 years	3 (2.8)	1 (2.8)	51 (53.7)	
>5 years	0 (0)	0 (0)	27 (28.5)	
Hydroxyurea therapy	73 (67.0)		0 (0)	<0.001*
Frequency of pain/12 months				
Nil pain/year	63 (57.8)	21 (58.3)	24 (25.3)	
1–2 VOC/year	29 (26.6)	13 (36.1)	41 (43.2)	<0.001
≥3 VOC/year	17 (15.6)	2 (5.6)	30 (31.6)	
Frequency of SCD-related admission/12 months				
Nil	55 (50.5)	17 (47.2)	65 (68.4)	
1–2	38 (34.8)	16 (44.4)	26 (27.4)	<0.05
≥3	16 (14.7)	3 (8.3)	4 (4.2)	
Frequency of SCD-related transfusion/12 months				
Nil	74 (67.9)	22 (61.1)	81 (85.2)	
1–2	29 (26.6)	12 (33.3)	13 (13.7)	<0.05
≥3	6 (5.5)	2 (5.6)	1 (1.1)	

*p-value refers to the level of difference between 109 Brazilian and 95 Nigerian patients.

patients from the São Paulo cohort were overweight or obese, 10 (9.2%) vs. 4 (4.3%) and taller for age, 17 (15.6%) vs. 8 (8.4%) (Figure 1).

Haematological and biochemical parameters

The mean haematocrit, MCV, MCH, MCHC and HbF were significantly lower in the Nigerian cohort (Table 3). However, the mean serum 25-OHD and zinc levels were higher. (Table 2). None of the Nigerian patients had severe vitamin D deficiency, and only 12.6% (12/95) had either deficiency or insufficiency (Figure 2). However, among São Paulo cohorts, 3.7% (4/109) had severe deficiency and 79.8% (87/109) had either deficiency [31.2% (34/109)] or insufficiency [48.6% (53/109)]. Only 16.5% (18/109) of the latter were vitamin D sufficient with values >30 ng/ml. The mean serum zinc levels of the Brazilian children were significantly lower (89.7±14.9 ng/ml) than 101.7±13.7 ng/ml for the Nigerian children, p<0.001. (Table 3). In addition, higher proportion of Brazilian children, 10.1% (11/109), compared with 1.1% (1/95) Nigerian children had low serum zinc levels, p=0.007, although the proportions with normal or high zinc levels were comparable, Figure 2.

Comparison of the 36 Brazilian patients not on hydroxyurea therapy with the 95 Nigerian patients who were also not on hydroxyurea (HU) therapy

In order to exclude hydroxyurea as a confounding variable, we compared the 36 Brazilian patients with SCD not on HU therapy with the 95 Nigerian patients who were also not on HU. (Tables 1 and 2). We found that the results were essentially similar to when all the 109 Brazilian patients were compared with Nigerian patients. The rates of significant pain episodes were still more common among the Nigerian patients, 74.8% (71/95) vs. 41.7% (15/36), respectively, p<0.001. Also, the rates of SCD-related hospitalization and transfusion were still more common among the Brazilian patients, p=0.025 and 0.012, respectively.

Table 2. Comparison of the nutritional parameters of Brazilian and Nigerian children with sickle cell disease

Nutritional parameters (mean±SD)	Sao Paulo, Brazil		Nigeria (95)	p-value*	p-value**
	All patients (109)	HU-naive (36)			
BMI-Z score	−0.40±1.43	−0.6±2.3	−1.04±1.35	0.001	0.004
HA-Z score	0.28±1.34	0.6±1.8	−0.52±1.33	0.003	0.006
MUAC (cm)	15.52±2.12	15.8±2.6	15.01±2.22	NS	NS
TSF (mm)	19.75±3.50	20.3±4.2	16.53±1.44	<0.001	<0.001
UAMA (cm^2)	7.06±2.10	6.8±2.5	8.01±3.68	0.027	0.012
UAA (cm^2)	19.53±5.66	20.4±7.5	18.27±5.66	NS	NS
UAFA (cm^2)	12.47±3.94	13.1±5.3	10.26±2.20	<0.001	<0.001
Fat percentage	63.80±4.65	64.3±4.1	57.67±6.33	<0.001	<0.001
25-OHD (ng/ml)	23.3±8.2	20.8±7.5	41.9±9.8	<0.001	<0.001
Zinc (ng/ml)	89.7±14.9	92.2±15.5	101.7±13.7	<0.001	<0.001

NB: BMI-Z score: body mass index, z-score; HA-Z score: height for age, *z*-score; MUAC, mid-upper arm circumference; TSF, triceps skinfold; UAMA, upper arm muscle area; UAA, upper arm area; UAFA, upper arm fat area.
Differences in the medians of BMI-Z score and HA-Z score were analysed with Mann–Whitney *U*-test. Others were analysed with independent sample *t*-test.
*p-value refers to the level of significant difference between all Brazilian and Nigerian patients.
**p-value refers to the difference between Brazilian patients who were HU-naive and Nigerian patients (who were also HU-naive).

The mean BMI-for-age *z*-score, height-for-age score, TSF, UAA, UAFA and fat % were significantly higher among the 36 Brazilian HU-naive patients, p<0.05 in each case. Similarly, the mean serum 25-OHD and zinc were significantly lower among the Brazilian compared with Nigerian patients, p<0.001.

Discussion

We compared the nutritional and some clinical parameters of two cohorts of children with SCD from Ilesa, Nigeria and São Paulo, Brazil, in order to examine the probable role of environmental factors on SCD phenotypes. Higher occurrences of underweight and short stature were observed among Nigerian children with SCD, while the occurrence of overweight or obesity was higher among the São Paulo cohort. In addition, prevalence rates of 25-OHD deficiency and insufficiency were higher among São Paulo children with SCD. These differences may be due to factors such as timing of diagnosis, unequal access to comprehensive care, dietary differences, climate and actual duration of exposure to sunlight.

In Nigeria, the rate of prescription of hydroxyurea is very low. In a recent survey of doctors in some dedicated SCD clinics in Nigeria, it was reported that less than ten of the 18 paediatric/adult SCD clinics prescribed hydroxyurea to individuals with SCD, and this was mainly only when the patients could afford it.[20] As at the present time, there is no national policy or guidelines on the use of hydroxyurea in individuals with SCD in Nigeria, and its use principally depends on the managing physician. However, in Brazil there are clear guidelines and policy on HU therapy in patients with SCD with the Brazil Ministry of Health approving its use in 2002.[21]

Newborn screening is a strategic component of comprehensive SCD care. About 85% of the Brazil cohorts were diagnosed in the newborn period, compared with none in Nigeria. It is known that early diagnosis significantly impacts on the severity of the disease. In this study, the average age at diagnosis for Nigerian children with SCD was 45.6 months, which is consistent with many previous studies.[22,23] This age at diagnosis is remarkably late when

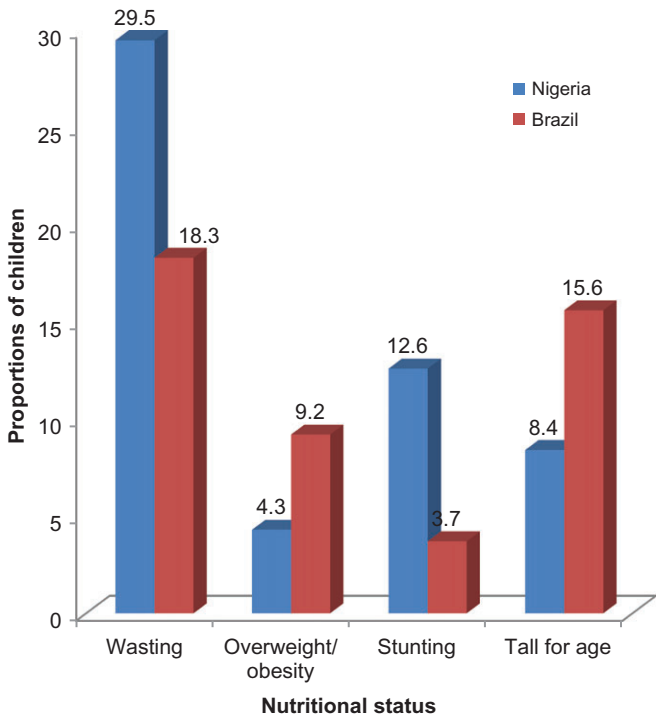

Figure 1. Comparison of the nutritional status of children with SCD from São Paulo Brazil and Ilesa, Nigeria.

Table 3. Comparison of the haematological variables of Brazilian and Nigerian children with sickle cell anaemia

Parameters	Brazil (109)		Nigeria (95)		p-value
	Mean±SD	Range	Mean±SD	Range	
Haematocrit (%)	26.8±4.8	18.1–48.1	23.5±3.6	12.7–31.4	<0.001
Leucocytes (×10^9/L)	12.8±6.2	3.9–47.4	14.5±5.2	4.3–36.5	0.044
Platelet counts (×10^9/L)	422±156	121–763	349±148	43.0–802.0	0.001
MCV(fL)	93.1±12.6	59.7–118.9	79.1±9.3	56.7–106.5	<0.001
MCH (pg)	31.8±5.2	20.2–41.3	26.1±3.5	17.3–33.5	<0.001
MCHC (g/dl)	33.8±2.5	16.9–38.3	33.0±1.6	29.4–35.9	0.016
HbF (%)	23.6±13.8	0–54.1	10.1±6.1	2.3–27.6	<0.001

Comparison was done by independent sample *t*-test.

compared to reports from most developed countries.[24–28] The diagnosis of acute chest syndrome, splenic sequestration and cholelithiasis was more frequently made among the Brazil cohort, while osteomyelitis was more common among Nigerian patients. It has earlier been reported that cholelithiasis is not frequent among Nigerian patients with SCD, probably because of their low dietary intake of cholesterol and refined fibre-depleted foods.[29] Also, most studies among Nigerian patients with SCD reported low prevalence of splenic sequestration, although the rate of splenomegaly is high,[30,31] and was found in one study to be about three times more common than in US counterparts (22.3% compared with 8%).[32] Malaria contributes significantly to persistent splenomegaly in Nigeria and in many long-standing cases, there is calcification. This may explain why acute sequestration is uncommon, although many affected children might have died before arrival in the hospital. Gumiero *et al.*, in their retrospective study of 225 Brazilian children with SCD at the Centro Infantil Boldrini, Campinas, São Paulo, reported that frequency of cholelithiasis was 45%, and a-third were diagnosed before the age of 10 years, even though about 50% were asymptomatic.[33] Reports of higher frequency of complications among Brazilian patients may, however, be a reflection of better documentation of these complications, rather than disease severity. The Brazilian cohorts probably had more follow-up visits than their Nigerian counterparts (in a bid to monitor HU therapy) or because of better health care utilization.

Similar to previous reports, a relatively high proportion of the children in both centres 23.5% (48/204) were wasted. Traditionally, this is due to high resting metabolic demands associated with underlying chronic anaemic states. Other factors, such as acute effects of vaso-occlusion and chronic organ damage, suboptimal nutrition, impaired intestinal absorption, micronutrient deficiency especially zinc deficiency, social factors, hormonal and endocrine dysfunction also account for the poor weight among the patients.[6,34,35]

In this study, Nigerian patients were thinner and had reduced linear growth for age than their Brazilian counterparts. On the contrary, more Brazilian children were overweight and obese. Over the past two decades, the average BMI percentile has been rising in the general paediatric population and even among those with SCD.[6] This observation has been attributed to

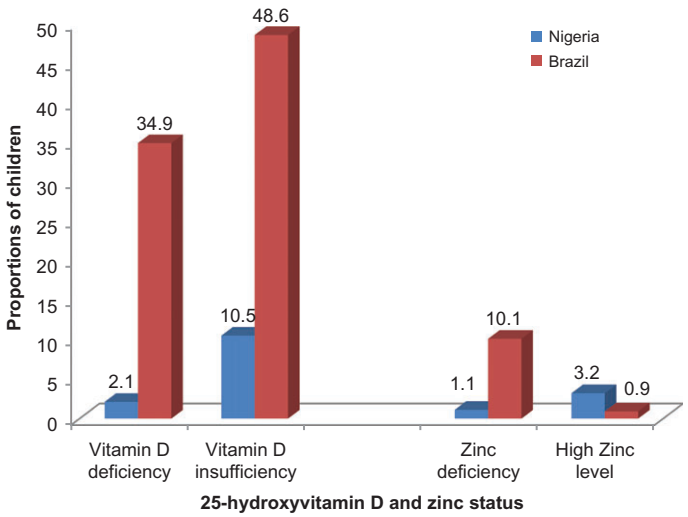

Figure 2. Comparison of serum 25-hydroxyvitamin D and zinc status of children with SCD.

increasing affluence with better nutrition, access to care and treatment advances like hydroxyurea therapy, as exemplified by the Brazilian patients in this study. It is therefore important to actively monitor the pattern of weight gain in these children, especially in those with specific SCD-directed therapies. The impact of elevated BMI on the morbidity and mortality of children with SCD must also be monitored. Appropriate nutrition and exercise regimens must also be formulated for them, in order to maintain a healthy weight throughout their lives.[6]

We also observed that mean serum 25-OHD levels were significantly lower, and vitamin D deficiency and insufficiency more prevalent among Brazilian children with SCD than the Nigerian patients. While none of the Nigerian patients had severe vitamin D deficiency (value less than 10 ng/mL), about 4% of the Brazil patients did. This obvious difference in the levels of vitamin D demonstrates the sizeable effects of latitude. São Paulo, like other cities in south-east Brazil experience longer period of cold weather. Hence, the time spent outdoors, and consequently

periods of exposure to sunlight are reduced and may explain this high prevalence of vitamin D deficiency. In a report by Peters *et al*. in 2009, less than a-third 27.9% (38/136) of Brazilian adolescents without SCD, in a rural town in São Paulo practised physical activity outdoors and 17.6% (24/136) of them regularly applied sunscreen.[36] The data also showed that reduced sunlight exposure alone may not completely explain high prevalence of vitamin D deficiency or insufficiency among those adolescents. Only 14.9% of the 136 in that study had adequate intake of daily vitamin D recommendation of 200 IU. Their mean vitamin D intake was 140 IU/day, and 60% had vitamin D insufficiency.[36] Low dietary intake of vitamin D rich foods and increased utilization of vitamin D for bone remodelling could have been the main contributory factors to the low serum vitamin D among those São Paulo adolescents.[36–38] In the light of its reported protective effects on musculoskeletal health, including pain regulation and immunomodulatory benefits, it is recommended that routine screening for vitamin D status and subsequent supplementation should be incorporated in the management plans for Brazilian patients with SCD.

A major limitation to this study was the determination of serum 25-OHD, zinc and haematological parameters in separate laboratories of the respective countries. Although similar standard procedures were followed in the two laboratories, accurate comparison of these variables could be jeopardized by inter-observer errors and differences in the prevailing laboratory working conditions. The results would have been more representative if they were done in the same laboratory. However, the outbreak of Ebola infection at the time of the study, which led to stringent regulations involved in the transportation of blood samples, hampered this.

Conclusions

In conclusion, although it is highly commendable that many Brazilian patients with SCD are now on specific SCD-targeted treatments, awareness should be made of the possibilities of these interventions leading to development of overweight and obesity. Hence, pragmatic efforts should be put in place to limit their rate of development. Meanwhile, improved SCD care, including early diagnosis and hydroxyurea therapy should be embraced among Nigerian patients, not only to reduce mortality, but also as a way of improving growth and nutritional status of these children. Given the lower income status of Nigerian population, it is likely that lower food intake, availability and quality may contribute to the difference in the nutritional states observed in this study. Our observation of low values of BMI-for-age *z*-score in both populations, indicators of very severe acute malnutrition in this sub-group of children, than in most other paediatric conditions would warrant continued specialized nutritional care by both paediatric clinical dietitians and physicians. Research is also needed to determine appropriate nutritional interventions and exercise regimens for patients with SCD, especially those on SCD-directed therapy, so as to maintain a healthy weight.

Authors' contribution: SAA and MSF conceptualized and designed the study. ADA and JAPB reviewed the study design. SAA executed and collected the data. JAPB also assisted in data collection. SAA, ADA and MSF analysed and interpreted the data. SAA wrote the initial draft. JAPB, ADA, MSF critically reviewed the manuscript for intellectual content and all the authors approved the final manuscript. ADA and MSF are the guarantors of the paper.

Acknowledgement: The authors would like to thank the Brazil National Council for Research (CNPq), Sickle Cell Support Society of Nigeria (SCSSN) and the Coordinator of Joint CNPq—Africa Countries Collaborative Postgraduate Research Training in Sickle Cell Disease, Profa. Dra. Marilda de Souza Gonçalves, for financial support and effective coordination.

Funding: This work was supported by CNPq [CNPq- 159581/2014–1 to SAA].

Competing interest: None declared.

Ethical approval: Institutional approval was obtained independently from the Ethics and Research Committee of the Hospital Universitario, Universidade Federal de São Paulo, Brazil [CAAE: 44676915.4.0000.5505] and Obafemi Awolowo University Teaching Hospital, Ile-Ife [ERC/2016/02/14]. Also, written informed consent and or assent was obtained from each study participant and their caregivers.

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