Nutritional Status of Children and Adolescents with Sickle Cell Disease

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Abstract
Sickle cell disease (SCD) is a public health problem that interferes in the nutritional status of children and adolescents. 

Objective: To describe the nutritional status and identify the factors associated with the growth deficit or obesity of children and adolescents with sickle cell disease.

Methods: Critical analysis of original articles published in Portuguese, English and Spanish in the electronic bases Medline, SciELO and LILACS with participants of 0 to 19 years old diagnosed with SCD.

Results: We identified 37 articles that describe low weight, short stature and overweight or obesity prevalence ranging between 3 and 100%, 8.2% and 24.0%, 1.6% and 22.4%, respectively. The associated factors to the growth deficit were the increase of resting energy expenditure, the presence of low bone density, the high prevalence of low zinc and D-vitamin plasma concentration, the low consume of calcium and D-vitamin, vessel occlusion crises, increased need of transfusions and hormonal amendments presence.

Conclusion: Amendments by weight and stature were frequent; however, we note an adjustment once the presence of overweight and obesity already exists in this group. The blood transfusion, the zinc supplementation and the regular use of hydroxyurea has shown benefit in the growth of children and adolescents with sickle cell disease.

Keywords
Sickle cell disease, Growth, Nutritional status, Obesity, Children, Adolescents

Introduction
Sickle cell disease (SCD) is a multisystem disease resulted from a monogenic mutation of the beta globin from hemoglobin that originates hemoglobin S (HbS) [1]. The term sickle cell disease encompass an amendments set which hemoglobin S is present, including sickle cell anemia (SCA; HbSS) and the others heterozygosis (HbSC, HbSD, S beta thalassemia, among others) [1]. SCD, the heritage disease with bigger prevalence in the world, is originally from Africa and can be found in a variety of countries [1].

Malnutrition between children and adolescents with SCD is described as common historically, making important to evaluate the growth and development in order to identify the growth speed decrease and the delay influential factors early once the low weight and short stature result in psychosocial [2] impacts exacerbating the clinical scenario.

Malnutrition in children and adolescents may be due to innumerable factors, such as the low consumption of food during the pain crisis or increased metabolism due to increased red blood cells turnover due to hyper hemolysis or the severity of the disease. Therefore, our initial hypothesis was that there would be a high prevalence of malnutrition in this group.

The objective of this review is to describe the nutritional status amendments prevalence and to identify...
associated factors to the growth deficit of children and adolescents with sickle cell disease.

**Methods**

A literature search using the Medline/PUBMED, SCOPUS, SciELO and LILACS electronic databases for studies published up to month year was conducted. The search terms sickle cell combined with nutrition, anthropometry, growth retardation, height and weight, Body mass index (BMI) and specific micronutrients (vitamin D and calcium, zinc, iron, and folic acid) were used. From a total of 1402 published studies, 37 with relevant data (21 cross-sectional and 16 longitudinal) were selected.

**Election criteria**

The articles were eligible when fulfilling the following criteria: 1) Having participants from 0 to 19 years old; 2) Have been published in Portuguese or English or Spanish; 3) Have informed reference standards to growth evaluation; 4) Have described some factors related to the growth (bone mineral density, body composition, linear growth, growth speed, calcium, zinc and vitamin D ingestion and/or serum levels, and/or different treatments effect during growth).

**Data collection process**

From the eligible studies were extracted the age

<table>
<thead>
<tr>
<th>Authors, year and country of study</th>
<th>Sample/Age (years)/Study type</th>
<th>Study objects</th>
<th>Anthropometric indicators/ Growth reference standard</th>
<th>Main Results and Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Singhal, et al. 1994 Jamaica [26]</td>
<td>132 children (44 HbSS, 44 HbSC and 44 Hb normal)/11 to 18 years (average: 17.9 HbSS, 17.9 HbSC, 17.9 Hb normal)/longitudinal and descriptive study.</td>
<td>Comparing the growth of adolescents with SCA vs. HbSC vs. health controls. Evaluating growth speed.</td>
<td>Height Western Indian University Hospital</td>
<td>Somatic peak age postponed by 1.6 years (0.9 to 2.3 years) in the SCA subjects, however the growth of SCA adolescents was normal and presented no difference in the height reached at 17.9 years. The growth rate did not delay in HbSC adolescents.</td>
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<tr>
<td>Warrier, et al. 1994 USA [29]</td>
<td>34 SCD children (22 HbSS, 4 HbSC, 3 HbSF and 5 had Sβ thalassemia)/6 months to 16.5 years/cross-sectional and descriptive study.</td>
<td>Determining the prevalence of mild and moderate malnutrition in patients with SCD.</td>
<td>Weight (W), Height (H) and Weight/height Waterlow classification, 1974 and NCHS, 1979</td>
<td>We observed weight loss (&lt; 80%) by Waterlow classification in 41% of boys and 25% of girls with SCD and height deficit (&lt; 90%) in 25% of boys and 25% of girls with SCD.</td>
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<td>Study</td>
<td>Participants</td>
<td>Methodology</td>
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<tr>
<td>dos Santos et al. 2018, 4:027</td>
<td>21 HbSS prepubertal children with SCA and short stature/age of children and GH deficient; 6.6 years; SCA and normal response to GH: 7.3 years; GHD isolated: 7.3 years</td>
<td>Cross-sectional and descriptive study.</td>
<td>Testing the hypothesis that SCA is associated with abnormalities of the IGF-1, IGFBP-3 and GH resistance axes.</td>
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<td>USA [14]</td>
<td>1998, Leonard, et al.</td>
<td>Observing the safety and efficiency of HU in children with severe SCD.</td>
<td>Height/age and Weight/age French sickle cell disease group. Basal concentrations of IGF-1 and IGFBP-3 were significantly lower in the group with SCA and deficient GH secretion. Children with SCA have lower significant IGF-1 production in response to GH, suggesting partial resistance to GH. BMI did not show any difference between the groups, but 9 of the 21 showed slower linear growth speed and lower concentrations of IGF-1 and IGFBP-3.</td>
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<td>France [36]</td>
<td>1997, de Montalembert, et al.</td>
<td>Weight/height NCHS, 1977</td>
<td>The HU had good tolerance in short and medium term. No difference in growth speed in any of the three groups of children and adolescents. Z-scores were similar at the beginning of the study, after 1 year and after 2 years of treatment, excluding the adverse effect of HU on growth in this cohort.</td>
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<tr>
<td>USA [14]</td>
<td>1998, Leonard, et al.</td>
<td>Weight and height University of South Alabama Comprehensive Sickle Center Clinics</td>
<td>44% of the children had low plasma Zn. They had a significant decrease in weight (-1.00 ± 0.15 ZS vs. -0.14 ± 0.13 ZS, p = 0.003) and height (-0.78 ± 0.15 ZS vs. -0.15 ± 0.14 ZS, p = 0.003) compared to those with normal Zn.</td>
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<tr>
<td>USA [41]</td>
<td>1999, Kinney, et al.</td>
<td>Weight and height NCHS, 1977</td>
<td>HU had no adverse effect on growth. At each 6-month interval, mean weight and height increased significantly (p &lt; 0.0001).</td>
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<tr>
<td>Brazil [27]</td>
<td>2000, Cipollotti, et al.</td>
<td>Weight and Height in standard deviation scores (SD). Collaboration Centers from USA and Europe.</td>
<td>100% of children and adolescents were underweight (NCHS). Average height lower than the NCHS standard at most ages, except for 7-year-old children. Only 15-year-old girls had a short stature.</td>
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<td>USA [42]</td>
<td>2000, Walters, et al.</td>
<td>Weight/height NCHS, 1977</td>
<td>Stature growth improved from -0.7 zs (before) to -0.2 zs after 48 months of transplanted.</td>
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<td>USA [8]</td>
<td>2001, Fung, et al.</td>
<td>Weight/age, Height/age and Height/age Adolescent: BMI/A NCHS, 1977</td>
<td>100% of children gained weight, height, fat and fat free mass. HU increased the Hb from 8.0 g/dL at the beginning to 8.4 g/dL at the end of the study, which may improve growth as well as reduce hypermetabolism.</td>
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<td>Brazil [23]</td>
<td>2001, Luporini, et al.</td>
<td>Weight/age and Height/age NCHS, 1977</td>
<td>Plasma concentrations of IGF-1 and IGFBP-3 were low in all patients with SCA. The positive relation between hematocrit and Hb F with total IGF-1, free/total IGF-1 and IGFBP-3 in patients with SCA showed that the growth delay of these patients may relates to intrinsic factors of the disease. Patients with the CAR/CAR haplotype had significantly slower growth speed compared to those with BEN/BEN.</td>
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<td>USA [41]</td>
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<td>Methods</td>
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<td>Silva, et al. 2002</td>
<td>Brazil [18]</td>
<td>100 children (73 with Hb SS and 27 with Hb SC) under 8 years old/longitudinal and descriptive study.</td>
<td>Evaluating the growth of children with HbSS and HbSC for a year and correlating it with hematological data.</td>
<td>Weight/age, Height/age and Weight/height NCHS, 1977 Malnutrition current in 8.2%, 9.6% and 1.4% of the SCA children when evaluated W/A, H/A and W/H, respectively. In children with HbSC were 14.8%, 3.7% and 0% respectively. The reduction of Hb in HbSS and HbSC children (mean of 7.5 g/dl and 10.2 g/dl, respectively) might relates to growth.</td>
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<tr>
<td>Barden, et al. 2002</td>
<td>USA [32]</td>
<td>66 children and adolescents (36 HbSS and 30 controls)/5 to 18 years (average: 11.3 ± 3.8 HbSS; 11.2 ± 3.2 controls)/cross-sectional and descriptive study.</td>
<td>Evaluating growth, nutritional status and body composition in children with SCA and without disease (control).</td>
<td>Weight, height and BMI Sickle cell Clinic of Western Indian University Weight, W/A, and H/A in zs were significantly lower in the SCA group. H/A: HbSS = 0.4 ± 1.1 zs vs. control = 0.5 ± 1.0 zs W/A: HbSS = 0.8 ± 1.1 zs vs. control = 0.3 ± 1.0 zs.</td>
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<tr>
<td>Singhal, et al. 2002</td>
<td>Jamaica [37]</td>
<td>72 children (41 HbSS and 31 controls)/3 to 6 years (average: HbSS: 4.1 ± 0.92, 4.2 ± 1.0; Controls: 4.1 ± 0.8 ± 4.1 ± 1.0)/cross-sectional and descriptive study.</td>
<td>Testing the hypothesis that energy consumption in relation to resting metabolic rate is lower in children with SCA than in control subjects.</td>
<td>Weight and height Study HUG-KIDS Children with SCA did not differ significantly from controls group of age, weight, body mass index and energy intake, but the resting metabolic rate was higher in children with SCA.</td>
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<td>Zemel, et al. 2002 USA [15]</td>
<td>42 HbSS prepubertal children/4 to 10 years (average: 7.1 years)/longitudinal with random intervention study.</td>
<td>Determining the effects of zinc supplementation on growth and body composition in children with SCA.</td>
<td>Weight/age, Height/age and BMI/A NCHS, 1977 15% had Zn deficiency (&lt; 10.7 mmol/L) and when they received supplementation of 10 mg/day they had 0.66 cm greater stature gain than the control.</td>
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<td>Wang, et al. 2002 USA [39]</td>
<td>68 HbSS children and adolescents/5 to 16 years/longitudinal with intervention study.</td>
<td>Evaluating the effect of HU on the growth of children with SCA.</td>
<td>Weight/age, Height/age and BMI/A NCHS, 2000 Treatment with HU had no adverse effect on height or weight gain or pubertal development. Weight during pre-treatment and treatment in the HUG-KIDS group was 11% to 27% higher than in the Sickle Cell Cooperative Study group. Height of children HUG-KIDS pre-treatment from 7 years old was 3 to 8 cm higher than height in the Cooperative Study of Sickle Cell Disease (p &lt; 0.05).</td>
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<td>Buison, et al. 2004 USA [16]</td>
<td>65 HbSS children and adolescents/5 to 18 years/ cross-sectional and descriptive study.</td>
<td>Examining the vitamin D status in children with HbSS and its relation to the time and dietary intake.</td>
<td>Weight/age, Height/age and BMI/A NCHS, 2000 Low serum vitamin D levels were highly prevalent in black children with SCA. Vitamin D status was associated with the year’s season and food intake. H/A, W/A and BMI/A in zs were not associated with the vitamin D status.</td>
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<td>Buison, et al. 2005 USA [12]</td>
<td>90 HbSS children and adolescents/4 to 19 years/ longitudinal and descriptive study.</td>
<td>Determining the impact of SCA on body BMC and body bone area in relation to height and body composition compared to the healthy individual.</td>
<td>Weight/age, Height/age and BMI/A NCHS, 2000 Low BMD (&lt; 3th percentile) for total body/age, bone area and BMC/age (14% and 9%, respectively). Low calcium intake by 75% and vitamin D by 77%. Serum vitamin D deficiency was 66%.</td>
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<td>Wang, et al. 2005 USA [19]</td>
<td>94 HbSS children and adolescents/2 to 16 years/ longitudinal and descriptive study.</td>
<td>Determining if long-term transfusion improves growth in children with SCA.</td>
<td>Height/age, weight/age and BMI Children’s Hospital Sickle Cell Integral Center, Oakland Children who received long-term transfusions had an increase in height, weight and BMI throughout the study (increase from 26.7 kg to 35.3 kg, from 127 cm to 140 cm, from 15.8 kg/m² to 17.4 kg/m², respectively) compared to children on standard treatment. Increased post-transfusion Hz (from 7.2 g/dl to 8.8 g/dl) can improve growth by decreasing energy expenditure.</td>
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<td>Lal, et al. 2006 USA [11]</td>
<td>25 HbSS children and adolescents with severe manifestations/9 to 19 years (average: 12.8 years)/cross-sectional and descriptive study.</td>
<td>Evaluating BMD and risk factors for low bone mineralization in children with SCA.</td>
<td>Initial and final weight and height. HCT Multicenter Study for sickle cell anemia. 33% had low BMD in the proximal femur and 56% in the lumbar spine. 60% low serum calcium (&lt; 1,300 mg) and low vitamin D level (&lt; 7.5 nM in 30%, &lt; 50 nM in 74% and ≤ 62.5 nM in 100% of those evaluated).</td>
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<td>Eggleston, et al. 2007 USA [40]</td>
<td>53 HbSS children and adolescents/&lt; 16 years/Multicentric, longitudinal and descriptive study.</td>
<td>Defining the risks and benefits of HCT.</td>
<td>Weight and Height Pediatric Hematology Outpatient Clinic, Duke University Medical Center. Small children with SCA did not show prejudice in growth by HCT; however, growth performs may decrease if HCT near or during the growth peak in adolescence. Boys in the HUG-KIDS (H) group are 2.7 kg heavier than the HCT group. Boys in the HUG-KIDS (Pre) group are approximately 4 cm taller the TCH group.</td>
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<td>Collett-Solberg, et al. 2007 USA [24]</td>
<td>22 children with HbSS/15 with height below the 25th percentile - mean age 10.45 ± 0.14 years and 7 with height above the 50th percentile-mean of 12.0 ± 3.63 years/cross-sectional and descriptive study.</td>
<td>Verifying if changes in the IGF-I axis are involved with growth deficit in children with HbSS.</td>
<td>Height/age, Weight/height, BMI/A NCHS, 2000. Lower levels of IGFBP-3 in children with short stature when compared to the normal growth group (p = 0.028). Children with SCA have abnormalities in the IGF-1 axis, which worsen with age. Mean height of normal growing children was not statistically different from the height of patient’s parents with short stature (p = 0.18).</td>
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<td>Zemel, et al. 2007 USA [20]</td>
<td>148 HbSS children/0 to 18 (average: 9.1 ± 4.7 years)/prospective, longitudinal and descriptive study.</td>
<td>Describing the longitudinal standards of growth in a group of children with SCA and identifying modifiable factors associated with below ideal growth.</td>
<td>Weight/age, Height/age and BMI/A NCHS, 2000. Growth in height, weight or BMI decreased in 84% of individuals; 38% were below the 5th percentile in one or more measurements. Puberty postponed in 1-2 years and mean age of menarche was 13.2 years. Bone age delayed by 1.3 ± 1.5 years in the age group of 10 to 15 years old.</td>
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<td>Fung, et al. 2008 USA [10]</td>
<td>80 HbSS children/ average: 11.2 ± 4.6 (4.5 to 19.0 years) /average: 10.0 ± 3.8 (4.5 to 19.1 years)/longitudinal and descriptive study.</td>
<td>Describing bone remodeling in children with SCA to determine if there is a relation between markers of bone remodeling and alteration of bone density and/or growth parameters.</td>
<td>Height, weight and BMC NCHS, 2000. Reduced BMC corrected for age in the last year of follow-up. Weight-for-age Z-score Males: -1.2 ± 1.1 (-3.2 to 1.1) Females: -0.5 ± 0.9 (-2.1 to 1.5) Height-for-age Z-score Males: -0.9 ± 1.1 (-3.2 to 1.7) Females: -0.1 ± 1.0 (-2.7 to 1.8)</td>
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<tr>
<td>Rhodes, et al. 2009 USA [9]</td>
<td>33 HbSS children/10 to 13 years/longitudinal and descriptive study.</td>
<td>Systematically studying the correlations between growth, hemoglobin and energy expenditure in children with SCA compared to healthy controls.</td>
<td>Weight/age, Height/age and BMI/A NCHS, 2000. Decrease of growth speed in children with SCA was independently associated with the decrease of Hb concentration and increase of total energy expenditure. There was no difference in weight or BMI at beginning of the study and after 1 or 2 years.</td>
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<td>Animashun, et al. 2011 Nigeria [30]</td>
<td>200 children (100 HbSS and 100 normal controls/1 to 10 years/prospective, cross-sectional and analytical study.</td>
<td>Determining the influence of socioeconomic status on the nutritional status of children with steady state SCA.</td>
<td>Weight/age, Height/age and BMI/A NCHS, 2000. Smallest range of weight and W/H in SCA patients than in the controls, however, there was no significant difference in height (p = 0.06) and in BMI/A (p = 0.12) among the SCA patients and controls (p &lt; 0.01). The mean values of body weight, height and BMI of the SCA subjects were consistently lower than those of the NCHS standards, and the difference increased with advancing age, affecting more males.</td>
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<td>Study</td>
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<td>Participants</td>
<td>Study Design</td>
<td>Objectives</td>
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<td>Dougherty, et al. 2011 USA [31]</td>
<td>151 children (35 HbSS and 103 controls)/5 to 3 years (controls average: 8.6 ± 1.8 and HbSS: 9.0 ± 2.2)/cross-sectional and descriptive study.</td>
<td>Analyzing the maximum muscle strength and peak power in children with SCA.</td>
<td>Height/age, Weight/height and BMI/A WHO, 2006 and 2007</td>
<td>Maximum muscle strength and peak power reduced in children with SCA compared to controls, in addition there was growth and body composition deficit. Z scores for height, weight and BMI significantly lower in children with SCA.</td>
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<tr>
<td>Souza, et al. 2011 Brazil [5]</td>
<td>161 children and adolescents/0 to 14 years (average: 7.4 years)/cross-sectional and descriptive study.</td>
<td>Evaluating the anthropometric nutritional status of children and adolescents with SCD.</td>
<td>Weight/height and BMI/A WHO, 2006</td>
<td>W/H: 2.2% of short stature, 3.6% of thinness, 94.6% of eutrophy and 1.6% of overweight BMI/A. 5.7% of thinness, 92.7% of eutrophy and 1.6% of overweight</td>
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<td>Nikhar, et al. 2012 India [28]</td>
<td>105 HbSS children/8 to 15 years (average: rural area 9 ± 2.1 years; urban area 8 ± 2.2 years)/cross sectional and descriptive study.</td>
<td>Performing a comparative study using anthropometric and hematological parameters in HbSS children from urban and rural areas of India.</td>
<td>Weight/age, Height/age and BMI/A WHO, 2007</td>
<td>Rural HbSS children presented lower weight compared to urban children.</td>
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<tr>
<td>Pinho, et al. 2012 Brazil [17]</td>
<td>12 HbSS children/ preschool and school/ cross-sectional and descriptive study.</td>
<td>Evaluating the anthropometric and dietary profile of children with SCA in a deprived area of the city of Januária (MG).</td>
<td>BMI NCHS, 2000</td>
<td>91.7% of eutrophy, 8.3% of thinness; 83.3% of suitable weight for age and 16.7% of low weight for age; 8.3% of short stature for age. Most of the children presented eutrophy, however, also inadequate dietary intake.</td>
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<td>Chawla, et al. 2013 USA [4]</td>
<td>675 HbSS children and adolescents/2 to 19 years (average: 10.8 years)/ multicentric/retrospective and descriptive study.</td>
<td>Determining the prevalence of underweight, normal weight, overweight and obesity in a multicenter study with urban population of children with SCA.</td>
<td>Weight, height and BMI NCHS, 2000</td>
<td>22.4% of overweight or obesity and 6.7% underweight. 38% of increase in the possibility of overweight/obesity for every 1 g/dL increase in Hb levels.</td>
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<td>Özen, et al. 2013 Turkey [13]</td>
<td>50 HbSS children and adolescents/&lt; 18 years (average: 13.1 ± 2.9 years)/cross-sectional and descriptive study.</td>
<td>Determining the frequency and risk factors for abnormalities in growth, development, puberty, thyroid function, bone and carbohydrate metabolism in children and adolescents with sickle cell anemia.</td>
<td>Height/age and Weight/height WHO, 2006</td>
<td>Weight and height of 24% were -2 SD below normal and 8% presented malnutrition. Growth hormone deficiency in 2% of female patients, and hypothyroidism in 6%; 11.1% had osteopenia and 2.2% had osteoporosis (vertebral), while 11.1% had osteopenia (femoral neck). Vitamin D deficiency occurred in 63.2% and insufficient in 18.4% of patients.</td>
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<tr>
<td>Bavle, et al. 2014 USA [33]</td>
<td>36 HbSS and HbSβ Thalassemia children/ retrospective and descriptive study.</td>
<td>Analyzing the growth of 36 children with HbSS and HbSβ Thalassemia in LTE, with average duration of almost 5 years.</td>
<td>Weight, height and BMI Evaluated the speed growth and comparison between groups. Cooperative Study of Sickle Cell Disease</td>
<td>Growth speed (cm/year) ♀ HbSS and HbSβ thalassemia (mean ± DP): 9.19 ± 2.98 (n = 16) vs. control: 8.46 ± 2.64 (n = 27) ♂ HbSS and HbSβ thalassemia (mean ± DP): 12.02 ± 3.41 (n = 8) vs. control: 8.70 ± 2.49 (n = 16).</td>
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studies, Weight/age (W/A) in 13, Weight/height (W/H) in 11 and Body mass index/age (BMI/A) in 9). We employed the National Center for Health Statistics (NCHS) reference standards in 19 studies and the World Health Organization (WHO) 2006-2007 in 6 studies regarding anthropometric indicators. In 13 studies, we used children with sickle cell anemia (SCA) data’s and in one study used Tanner classification of 1976.

Prevalence of nutritional status changes
The height and weight deficit values vary from 8.2% to 34.9% and from 3.7% to 100% respectively, and overweight vary from 1.6% to 22.4%. The emergence of weight and height compromise seems to be early, as we see in Stevens, et al. [3], which observed weight and height deficit before the age of 2 years on children with SCA. However, we observed overweight/obesity pres-

group of the individuals, the nutritional status parameters, the prevalence of nutritional parameter classifications and the described factors that interfered in the nutritional status.

Results
Study characteristics
Predominantly the studies type was descriptive (n = 34) with great variation in the sample number (from 8 to 675 participants) and in age (between 0 to 19 years old) (Table 1).

Study results
The studies applied varied the growth evaluation parameters. In addition, we observed the use of weight in 15 studies; of stature in 18 studies and of anthropometrics indicators in most studies (Height/age (H/A) in 17 studies, Weight/age (W/A) in 13, Weight/height (W/H) in 11 and Body mass index/age (BMI/A) in 9).

We employed the National Center for Health Statistics (NCHS) reference standards in 19 studies and the World Health Organization (WHO) 2006-2007 in 6 studies regarding anthropometric indicators. In 13 studies, we used children with sickle cell anemia (SCA) data’s and in one study used Tanner classification of 1976.

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ence mostly as of 2011’s published studies [4-7].

**Associated factors with nutritional status**

The associated factors with growth deficit were resting energy expenditure (REE) [8] increase; Low mineral bone density [9-13]; Plasma concentration of micronutrients decrease [11,13-17]; Low concentration of hemoglobin [4,5,9,18-20]; The low food intake; Hormonal alterations [13,21-24], Vessel occlusion crises and increased need of transfusion [25].

However, the associated factor with overweight was the biggest Hb concentration, indicating the best disease prognosis, according to Chawla, et al. study [4]. Bone mineral density (BMD) was assessed in five studies. Dietary intake of micronutrients in 4 studies (vitamins B12 and A in 1 study, vitamin C in 1 study, vitamin D and calcium (Ca) in 3 studies, zinc (Zn), iron (Fe) and folic acid in 1 study). Zn plasma concentration in 2 studies. Serum levels of Ca in 2 studies and vitamin D in 3 studies.

The presence of low BMD varied between 14% and 56%; Low calcium and vitamin D intake varied between 48% and 75%; Low serum zinc concentration between 15 and 44% moreover vitamin D between 66% and 100%.

**Discussion**

This review found the following results: a) The magnitude of short stature ranged from 8.2% to 24% and low weight from 3.7% to 100%; b) The presence of overweight or obesity is already detected between 1.6% and 22.4%; c) The factors associated with the growth deficit described in the articles were: Increased resting energy expenditure around 17% and nutritional deficiencies (low calcium and vitamin D intake between 48% and 75%; Low serum zinc concentration between 15 and 44%, vitamin D between 66% and 100%); d) Other factors described (presence of low bone mineral density between 14% and 56%, low Hb concentration, transfusions frequency and onset, complications frequency such as vessel occlusion and hand-foot syndrome, and the presence of hormonal alterations.

**Abstract of evidences**

The weight and length at birth of the child with SCD are usually normal and change until the end of the first year of life, culminating with low weight and short stature in childhood [2]. However, the child can reach normal height in adolescence, because the growth spurt occurs late due to delay in the closure of the epiphyses, which allows the recovery of stature in the adult phase [2,26]. As for short stature, it usually was associated with low bone mineral density [10-12] and the deficiency of some micronutrients such as zinc [15,16], calcium [12] and vitamin D [11,12].

The Kazadi study [25] noted that the increased risk of short stature was related to a history of hand-foot syndrome and to the need for more than three transfusions per patient, in addition, malnutrition with vessel occlusion crises higher to two per year and the need for the first blood transfusion before 12 months old.

Evaluation of growth used different reference standards, with the NCHS growth curve being the most used, since they were twenty-one studies prior to the publication of the 2006 and 2007 WHO growth curve. However, regardless of the standard used, the weight and height deficits were prevalent in children and adolescents with SCD [3-7,13,14,17,18,20,25,27-33].

In contrast, the predominance of normal and the presence of overweight or obesity observed in the more recent studies [4,6,7,17,19] changes the nutritional profile of this group. These findings are important and possibly results of improved health care for people with sickle cell disease and changes in diet for the world’s population.

The existence of extremes, namely of growth deficit or overweight/obesity, reinforces the need to monitor nutritional status, once both may aggravate the pathological conditions of children and adolescents with SCD, favoring a higher contraction of infections [2,34] and respiratory complications [2,34].

Some factors affected nutritional status, such as clinical variables (hemoglobin concentration), disease progression (cardiac output and erythropoiesis increase, favoring REE increase), nutritional factors (low food intake and micronutrient depletion) and the type of treatment implemented.

In Bennett’s study [35] four factors identified contributed to the delayed growth of children with SCA: Endocrine dysfunction, hypermetabolism, inadequate food intake, and micronutrient deficiencies, which reinforces the results found in this review.

The increase in REE [8,36] directly contributes to the increase in energy needs, since it corresponds to 65% to 70% of the total daily energy expenditure [37]. Therefore, it can lead to the growth deficit only or when associated with a decrease in food consumption, common in hospitalized children for allergic crisis [8]. Individual nutritional monitoring of the child should be implemented in order to minimize hyperoxia, increase daily energy consumption and, consequently, restore nutritional status.

Furthermore, lack attention in the monitoring of essential micronutrients for child growth, which are commonly low in consumption, such as calcium [11,12] and vitamin D [12,16] or that were in low serum concentration, such as zinc [14,15] and vitamin D [11,12,16] increases the risk of malnutrition. Therefore, they need to be monitored during the nutritional follow-up. Micronutrient depletion contributes to the onset of low bone mineral density [11,12], of delays in skeletal maturation and growth deficit [15]. The importance of this monitor-
ing was evident in the randomized clinical study which, when supplementing children with SCA with 10 mg of elemental Zn for 12 months, showed significant stature gain [15].

Adequate clinical follow-up of the person with SCD usually results improvement in hemoglobin concentration. Adequate levels of hemoglobin in these patients, as evidence shows, avoid important complications such as aplastic crisis, splenic sequestration crisis, stroke, among others [27]. In addition, it was also observed that children with lower P/I were those with lower Hb concentration [19]; And those with higher Hb concentrations [5] were associated with overweight and obesity, as well as with the use of hydroxyurea (HU) [8,38] and continuous blood transfusion [21]. Endocrine compromise is also one of the factors that interferes with these children’s growth. Those with SCD and low stature had low basal IGF-1 [21-24] concentrations and/or IGF-binding protein-3 (IGFBP-3) [21,23,24] and/or growth hormone (GH) deficient [21-23]. The deficiency of these hormones relates to slow growth and short stature in children with SCA, however, the Ca, the micronutrient involved in growth, was normal in evaluated children [21]. Soliman, et al. [22] identified the presence of empty turmeric saddle in all children who had GH deficiency, which is suggestive of ischemic lesion in the pituitary gland. Therefore, in the persistence of nutritional deficits it is necessary to investigate these hormones.

In relation to the studied treatments [8,19,38-40], these seem to positively impact on growth and development by improving the clinical picture of the disease. However, should be noted that the studies with HU [8,38,39,41] had a small sample number, ranging from 8 to 84 patients and short follow-up periods, from 4 months to 2 years. The results with the HU use in the nutritional state ranged from no difference in growth velocity [36] to weight gain, height [8,39] and fat free mass [41].

Another treatment, hematopoietic cell transplantation (HCT) seems to not impair growth [40,42], but it is not advisable to perform it in the next period or during the growth spurt of adolescence [40,43]. The association between growth deficiency and HCT may be related partly to gonadal toxicity due to the busulfan (BU) doses administered. The likelihood of growth speed reduction is higher if the inhibitory effect of BU on gonadal function is exercised before the completion of the pubertal growth peak or the institution of hormone replacement therapy [40]. Despite this study [40] did not describe growth improvement with transplantation, it brings important contributions in guiding the most appropriate moment for its realization, in order to avoid losses in growth. Walters, et al. [42] observed improvement in linear growth after transplantation, however, they described the adverse effect of BU on the ovarian function of five of seven girls evaluated with age above 13 years old.

The different treatments evaluated presented benefits or minimized the growth deficit; However, more studies are necessary to evaluate the late effects of each type of treatment. Early diagnosis and appropriate treatment can reduce or avoid complications of the disease, so it is extremely important to follow up with professionals from different specialties, as well as the family and the community to know about the disease and its basic care [44].

The present study evidenced a high prevalence of weight and height deficits in this group, existing, although, the presence of overweight/obesity in those with better clinical conditions. The main factors associated with the growth deficit were described, which may lead to a more adequate clinical practice, since it makes it possible to prevent the occurrence of both growth and obesity deficits. Therefore, evidence-based interventions designated to prevent and minimize these changes in nutritional status.

Limitations

The studies analyzed have several methodological limitations. First, most studies have a wide breadth of age, mixing infants, preschoolers, schoolchildren, adolescents, and young adults. Secondly, they did not investigate the action of different physio pathological and therapeutic aspects in the same group of children and adolescents. Third, there was a variability of several growth reference standards, which did not allow the comparison of the data. Finally, there was a predominance of descriptive cross-sectional studies, which did not allow to conjecture a possible time line between the associated factors and the compromising of nutritional status.

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Competing Interests

The authors declare that they have no conflict of interest.

Author’s Contributions

Design: Cláudia dos Santos Cople-Rodrigues; Samara Agda dos Santos; Data analysis and interpretation: Samara Agda dos Santos; Cláudia dos Santos Cople-Rodrigues; Cecília Lacroix de Oliveira; Review and approval of the final version of the article: Cláudia dos Santos Cople-Rodrigues; Samara Agda dos Santos; Cecilia Lacroix de Oliveira; Paulo Ivo Cortez.

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