

## Sickle cell disease complications and BMI percentiles of pediatric patients

**ABSTRACT:** BMI percentile is a good index of nutritional status among pediatric patients. Yet there is a dearth of information about the relationship between this important anthropometric parameter and specific severity indices among pediatric patients. The study is designed to explore the possibility of such a relationship. **Methods:** Pediatric study participants were divided into test [HbSS, HbSC] and control [HbAA] groups. The questionnaire was administered to obtain information on age, gender, and clinical features of the disease [pain frequency, leg ulcer, priapism]. The anthropometry indices were determined. BMI as well as BMI percentiles were calculated. Data were summarized using relative frequency, mean, and standard deviation while analysis of variance, LSD post hoc tests and Chi-squared tests were used for inferential statistics. Significant levels were set with  $P < 0.05$ . **Results:** There were significant differences in the body weight, height and BMI of HbAA, HbSC and HbSS. The distribution of the BMI percentiles for the three genotypes showed that 5% of HbAA, 20% of HbSC, and 35.7% of HbSS were in unhealthy categories. The occurrence of leg ulcers and priapism among the two SCD genotypes was 0% and 3.57% respectively. The Chi-square tests showed a significant difference between BMI percentiles ( $X^2=72.51$ ;  $P<.001$ ) or painful episodes ( $X^2=15.992$ ;  $P=.003$ ) and hemoglobin genotypes [HbSS, HbSC]. Among SCD patients there was a relationship between BMI percentiles and pain frequency ( $X^2=50.59$ ;  $P<.001$ ). **Conclusion:** The study suggests that SCD impacts BMI percentiles. Also, the frequency of occurrence of priapism and leg ulcers varied widely, indicating that priapism among the SCD patients may be a more common SCD complication than leg ulcer in the region. The fact that there was a higher frequency of pain

among HbSS than HbSC suggests a bias in distribution of pain frequency in the 2 hemoglobinopathies.

**Keywords:** BMI percentile, sickle cell disease, disease severity markers; pediatric patients

## 1.0 INTRODUCTION

Sickle cell disease (SCD) is a clinical condition that is characterized by the presence of sickle-shaped and fragile red blood cells [1,2]. It is a genetic, autosomal recessive blood disorder with high morbidity and mortality rates and the commonest monogenic hemoglobinopathy [3,4]. The term sickle cell disease (SCD) is used when the hemoglobin (Hb) S gene alone or in conjunction with another abnormal beta ( $\beta$ ) globulin gene has been inherited by an individual. A substitution of a single amino acid in the beta globulin chain of the adult hemoglobin molecule, results in the formation of either hemoglobin S, C, D, or E depending on amino acid substitution [5,6]. Sickle cell anemia (SCA) is a homozygous state caused by a point mutation in the beta globulin gene in which glutamic acid is replaced by valine at the sixth position, resulting in the synthesis of a variant of hemoglobin known as hemoglobin S (HbS) which is a structural variant of the normal adult hemoglobin (HbA) [5]. At low oxygen tension, HbS polymerizes in the red blood cells [7,8] which makes the erythrocyte membranes more rigid. The membrane's morphology and function are thereby compromised. Hence, the transport of oxygen is impaired, and a deposition of these red blood cells in the endothelial wall occurs. These cascades of events can result in chronic inflammation, difficulty in microcirculation, painful episodes, hospitalization, stroke, or other complications [9-13].

A definitive cure is not currently available to the majority of affected individuals in the developing world, but most current therapies are only directed at symptom management and do

not alter the natural history of the disease [14]. These therapeutic/symptom-management options include adequate nutrition, pain control, hydration, prevention of infections, and precautions against adverse weather conditions. Of all these options, the assessment of nutritional level that impacts and provides information about a wide range of metabolic processes in diseased states [15-17] can be inferred from BMI percentiles. In SCD, such metabolic alterations may give rise to conditions like vaso-occlusive crisis (VOC) with severe and frequent pain and inflammation [18-21]. BMI percentile has been recommended as an appropriate marker for assessing nutritional status in children [17].

While it is well established that BMI percentiles play an essential role in the pathophysiology of SCD; there is insufficient empirical evidence linking BMI percentiles with specific severity indices such as pain frequency, leg ulcers, and priapism. Hence, the study is designed to investigate the role of this important anthropometric index in the gravity of specific disease markers among children with SCD.

## **2.0 MATERIALS AND METHODS**

### **2.1 Study participants and ethical issues**

A total of 63 children aged 17 years or below were enrolled in the study, with 20 of them being the control, the rest were divided into homozygous (HbSS) and heterozygous (HbSC) sickle cell disease groups through a multi-stage random sampling technique. The study design was cross-

sectional and comparative between test non-SCD control [HbAA] and SCD patients [HbSS, HbSC]. The enrollment sites were the Haematology and Outpatient clinics of Obafemi Awolowo University Teaching Hospital Complex (OAUTHC) Ile-Ife; Wesley Guild Hospital, Ilesha; and Osun State University Teaching Hospital Osogbo (UTH), Nigeria. All participants were age and gender-matched. Before the participant enrollment, ethical issues relating to the study had been resolved by seeking and obtaining ethical approval from the Osun State Ministry of Health, Osogbo. The ethical issue relating to the study participants was addressed by obtaining informed consent (written) from their parents, guardians, or caregivers as well as getting the assent of children who were 7 years and above. All participants were assured that strict confidentiality of all qualitative and quantitative data derived from the study would be maintained.

The participants in the control group were enrolled at the Outpatient Department (OPD) where each of them came in for minor medical complaints such as minor aches and pains, medical certificate of fitness for school enrollment, etc. A detailed medical history of all participants was taken. The hemoglobin genotype of each participant was determined using the cellulose acetate hemoglobin electrophoresis. Physical deformities that can affect the accurate measurement of BMI, as well as any other chronic illness that affects physical growth such as bronchial asthma, congenital heart disease, chronic renal failure, diabetes mellitus, or malignancies, were additional disqualification criteria.

Individually, the questionnaire was administered to the participants to obtain information on age, gender, and clinical features of the disease [especially frequency of occurrence of leg ulcer, priapism, and pain frequency] in the 3 months before the participants were enrolled for the study.

## **2.2 Determination of anthropometric markers**

The anthropometry indices- the weight and the height of each participant were determined with a combined measuring instrument Health Weighing Scale and Stadiometer (RTZ-120A, HECOS, China) with error margins of 0.1 kg and 0.1 cm for weight and height respectively. Each time before the measurements were taken, scales were standardized using known weights to ensure reliable and exact measurements. Gender, age, height, and weight of the child at measurement were employed to calculate BMI percentiles, using the SAS program provided by the Centre for Disease Control (CDC) [22]. The BMI was calculated by the formula:  $BMI = \text{Weight (Kg)}/\text{height (m}^2\text{)}$ . The classification of nutritional status was based on underweight [BMI less than the 5th percentile], healthy weight [BMI of 5th up to less than 85th percentile], overweight [BMI of 85th to less than the 95th percentile], and obese [BMI equal to or greater than the 95th percentile].

### **2.3 Statistical analysis**

Data were analyzed using the Statistical Package for Social Sciences (SPSS) version 26. (Armonk, NY: IBM Corp). Continuous variables such as height, weight, and BMI, were expressed as mean and standard deviations. Comparison of means of continuous variables was done using analysis of variance (ANOVA). LSD post hoc tests were carried out for paired comparison. For categorical variables, the Chi-squared test (Fisher's exact test, if indicated) was used for the test of significance. Significant levels were set with  $P < 0.05$ .

### **3.0 RESULTS**

The results of body weight, height, and BMI of HbAA, HbSC, and HbSS are presented in Figures 1-3 below. Significant differences were recorded for each of the anthropometric parameters when HbAA, HbSC, and HbSS were compared. In either homozygous or

heterozygous sickle cell disease state, the three anthropometric parameters were significantly lower compared with non-SCD control. ANOVA showed that there was a significant difference when the BMI of the three hemoglobin genotypes was compared [ $F= 15.26$ ;  $P= <.001$ ]. The distribution of the BMI percentiles for the three genotypes of hemoglobin was HbAA (overweight- 5%, healthy weight- 95%; Underweight- 0%); HbSC (overweight- 6.7%, healthy weight- 80%, underweight- 13.3%); and HbSS (overweight- 10.7%, healthy weight- 64.3%, underweight- 25%). There was no incidence of leg ulcers among the two SCD genotypes. Only 3.57% of HbSS participants but none among HbSC reported the occurrence of priapism.

After the automatic recording of data, ANOVA was carried out to determine whether there were significant differences in BMI percentiles of different groups; results showed that there was a significant difference when the three groups were compared ( $F = 3.772$ ,  $P = .029$ ). While there was no difference between HbAA and HbSC ( $P= .461$ ) as well as between HbSC and HbSS ( $P= .439$ ), there was a significant difference in the BMI percentiles of HbAA and HbSS ( $P= .022$ ). Figure 4 shows the BMI percentiles of children with HbAA, HbSC, and HbSS genotypes.

The Chi-square test showed there was a significant difference when the hemoglobin genotypes (HbAA, HbSS, HbSC) were related to BMI percentiles ( $X^2=72.51$ ;  $P = <.001$ ). Also, the Chi-square test revealed there was a significant difference ( $X^2 = 15.992$ ;  $P = .003$ ) in the occurrence of pain among SCD patients, with HbSS having a higher frequency of pain than HbSC. Seventy percent of HbSS reported the occurrence of pain at least once monthly as against 60% among the HbSC participants. Additionally, among SCD patients there was a relationship between BMI percentiles and pain frequency ( $X^2=50.59$ ;  $P=<.001$ )

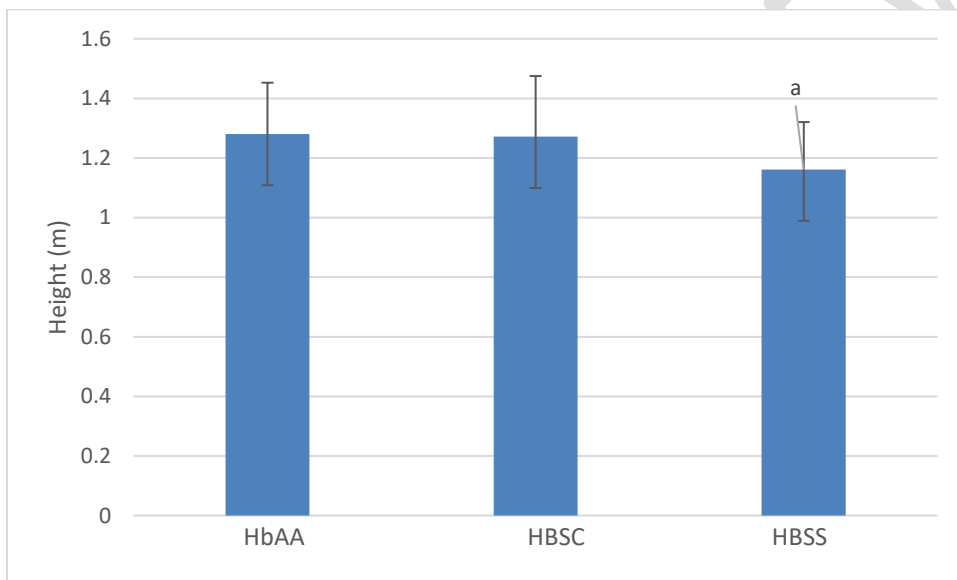


Figure 1: Standing height of children with HbAA, HbSC, and HbSS genotypes are presented as mean  $\pm$  standard deviation

a- denotes a significant difference between HbAA and HbSS ( $P < .05$ )

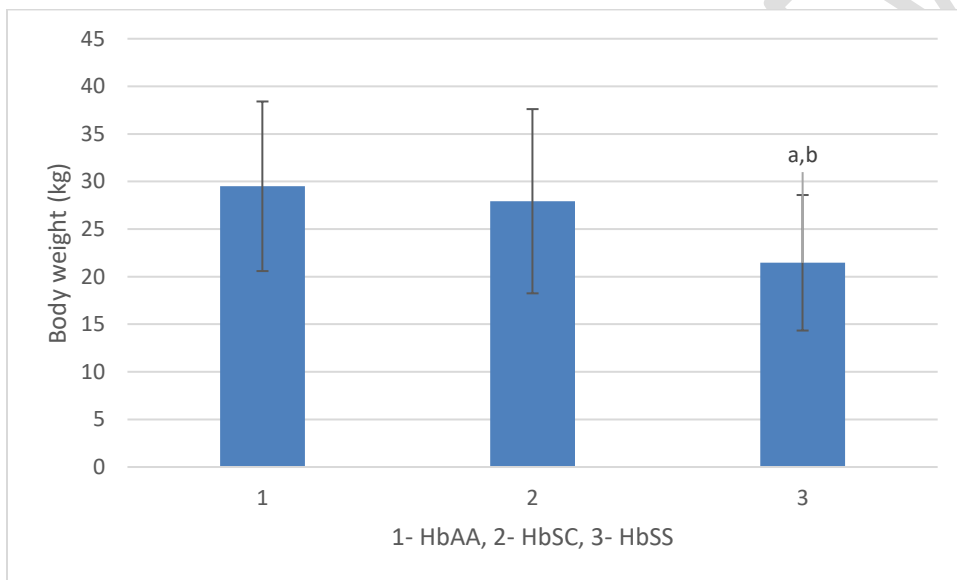


Figure 2: Body weight of children with HbAA, HbSC, and HbSS genotypes are presented as mean  $\pm$  standard deviation.

a and b- denote significant difference between HbAA and HbSS and between HbSC and HbSS respectively ( $P < .05$ ).

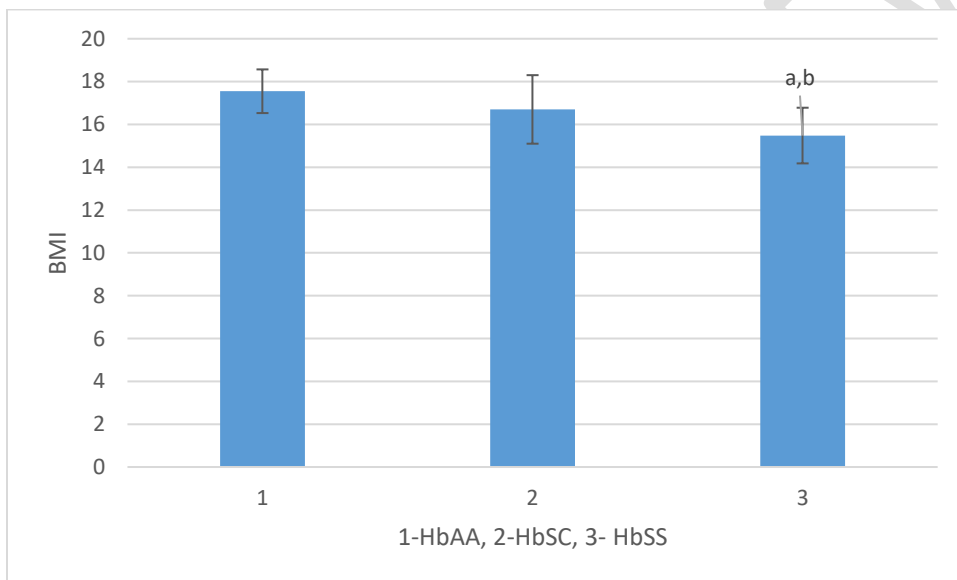


Figure 3: BMI (body mass index) of children with HbAA, HbSC, and HbSS genotypes are presented as mean  $\pm$  standard deviation.

a and b- denote a significant difference between HbAA and HbSS and between HbSC and HbSS respectively ( $P < .05$ ).

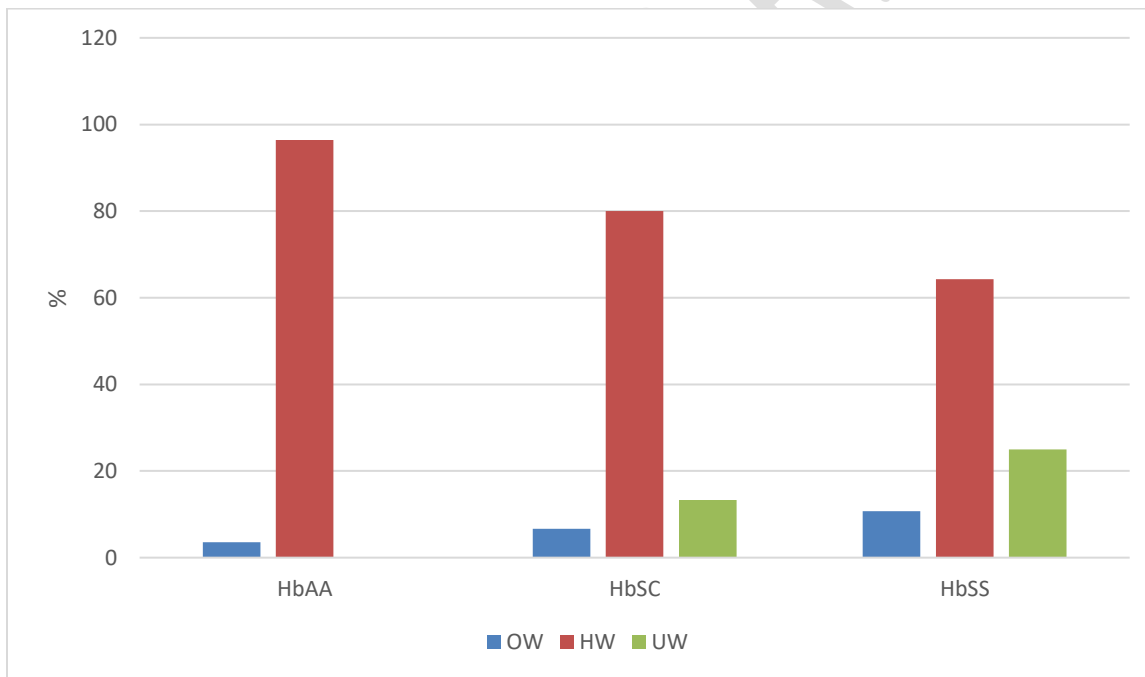


Figure 4: The BMI percentiles of children with HbAA, HbSC, and HbSS genotypes expresses as relative frequency.

Abbreviation: OW- overweight (85<sup>th</sup> percentile to <95<sup>th</sup> percentile); HW- Healthy weight (5<sup>th</sup> percentile to <85<sup>th</sup> percentile); UW- underweight (<5<sup>th</sup> percentile)

#### 4.0 DISCUSSION

The role or involvement of nutrition in disease processes or altered physiology is well documented [24,25]; nutrition which impact anthropometry and BMI percentiles in children. Results of the study showed that the BMI percentiles [and by implication nutritional status] of test participants differed significantly from that of the control. More children in the control group (95%) were in the healthy weight category than those in SCD [HbSC-80%; HbSS- 65%] groups. Similarly, the results of Chi-square lent credit to this opinion, as there was a significant difference when the relationship between BMI percentiles and hemoglobin genotypes [HbAA versus HbSC/HbSS] was tested, signifying that hemoglobin genotypes may influence BMI percentiles. This is even though only the BMI of HbSS but not that of HbSC was significantly different from that of the control.

The significantly altered BMI percentiles of SCD children compared with control is not unexpected, aside that patients with SCD have greater than average requirements for calories and micronutrients [26,27] impacting BMI percentiles. The elevated rate of red cell turnover, an important peculiarity of SCD, stimulates a state of hypermetabolism. Increased protein turnover, increased myocardial activity, and production of proinflammatory cytokines were portrayed as the biochemical and physiological dynamics that aid hypermetabolism [28]. Generally, it is presumed that the nutritional requirements recommended are not sufficient to meet the needs of patients with SCD given their increased energy expenditures and other abnormal metabolic demands.

Additionally, researchers such as Hibbert and colleagues in various attempts [29-31] as well as others, had earlier demonstrated that marked hypermetabolism is of considerable concern in SCA. They linked hypermetabolism with erythropoiesis and increased urea kinetics (a result of

protein catabolism). In SCD, nutrients are channeled toward rapid red cell synthesis and replenish hemolyzed sickle red cells being continually removed from the circulation. This anabolic/catabolic derangement drastically enhances the energy requirement and reduces the accessibility of nutrients for development during childhood and for sustaining adequate muscle mass during adulthood.

Interestingly, HbSS participants in the healthy weight category [BMI percentile 5-85%] in the study constituted only 64.30% as against 80.60% (Hall *et al.*, 2018) and 70.10% (Chawla *et al.*, 2013) obtained from studies carried out in the United Kingdom and the United States of America respectively. In addition, the healthy weight category for HbSC for the study of 80% is different from that of HbSS UK children 73.63% (Hall *et al.*, 2018). More fascinating is that most of the HbSS and HbSC SCD children in the UK study with abnormal BMI percentiles were in the overweight category. In the overweight category, Hall *et al.* [2018] recorded 13.20% and 25.27% for HbSS and HbSC respectively as against 10.7% [HbSS] and 6.7% [HbSC] observed in the study. The high percentage of 25% [HbSS] and 13.3% [HbSC] for the underweight study as against 6.6% [HbSS] and 1.1% [HbSC] recorded by Hall *et al.* is another feature that distinguished the present study from that of Hall *et al.* [2018]. These discrepancies in data obtained from different regions suggest that it may not be the disease alone that is responsible for abnormal BMI percentiles of SCD pediatric patients. The three studies were carried out in areas of different socio-economic zones.

Meanwhile, the dissimilarity in result outcomes (of BMI percentile) from the various regions may not necessarily be due to socio-economic level alone, even though socio-economic status is a very important determinant of BMI percentiles and the three study locations belong to different economic levels, yet other factors such as the differences in SCD haplotype has been recognized

to determine the frequency and severity of many complications or metabolic events associated with SCD.

Take for instance leg ulcers, its incidence among SCD patients varies widely: in the USA – 2.5% to 25%; Jamaica- 75%; Ghana/Nigeria- 10% [34]. According to Babalola *et al.* [34], such wide variation (2.5% - 75%) may be the result of differences in the SCD haplotype of these 3 regions. Global distribution of sickle-cell anemia haplotypes among nations with a high prevalence of the disease revealed that there are 5 distinct  $\beta$ -globin haplotypes among patients with sickle-cell anemia, which are Benin, Cameroon, Central African Republic/Bantu, Senegal and Saudi Arabia/India [35]. The 10% incidence of leg ulcers among Nigerians and Ghanaians according to Babalola *et al.*, [34], and the case of no incidence [0%] for the present study are not in agreement and therefore rule out a possible role for haplotype or economic level as a determinant of leg ulcer incidence among SCD children. This assumption is reasonable bearing in mind that the study participants (Ghana, Nigeria) were people with the same Benin haplotype and within the same low-income category.

According to Abd Elmonein *et al.* [36] previous reports indicated that the mean age at which priapism occurs is 12 years and that by 20 years of age nearly 90% of males SCD would have experienced priapism at least once. Meanwhile, with respect to the study only 3.57% had experienced priapism, which suggests that priapism is less common among pediatric SCD patients in Osun state. Regarding pain frequency, Abd Elmonein *et al.* [36] observed painful episodes among SCD children which are in agreement with the study in which 70% and 60% of HbSS and HbSC respectively reported occurrence of pain at least once monthly. An observation which is not at variance with earlier submissions among SCD adult patients when both disease severity and biochemical indices were used as markers of study [37,38].

### **Limitation of study**

While the study has shed light on the nutritional status of SCD pediatric patients through the use of BMI percentiles, administration of food frequency questionnaire [FFQ] to participants would have been helpful.

### **Contribution**

This study contributes to the existing literature on SCD, anthropometry and BMI percentiles [a marker of nutritional status] among pediatric patients. It invigorates ongoing discussion on how the comprehensive care of an individual with SCA sometimes may require monitoring of growth, which no doubt will assist in facilitating prompt and early diagnosis of growth abnormality and the need for nutritional intervention especially as it has been shown that this may vary from one genotype of SCD to another.

### **Conclusion**

The study suggests that BMI percentiles of SCD vary from non-SCD participants and that more HbSS patients were in the underweight category than HbSC. Additionally, there seems to be rare occurrence of priapism among the participants as well as no incident of leg ulcers. The high occurrence of pain episodes among the SCD patients suggests that it may be a more common SCD complication than leg ulcer and priapism in the region. The fact that there was a higher frequency of pain among HbSS than HbSC suggest a bias in distribution of pain frequency in the 2 hemoglobinopathies.

Ethical approval and Consent

Before the participant enrollment, ethical issues relating to the study had been resolved by seeking and obtaining ethical approval from the Osun State Ministry of Health, Osogbo. The ethical issue relating to the study participants was addressed by obtaining informed consent (written) from their parents, guardians, or caregivers as well as getting the assent of children who were 7 years and above.

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