Sickle Cell Disease and Obesity in the Pediatric Population in Mississippi

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Abstract

Background: Children with sickle cell disease (SCD) have higher resting basal metabolic rates than healthy peers and have historically been underweight. Current treatments increase patients' hemoglobin (Hb) level and decrease reticulocytosis, which may in turn decrease patients' basal metabolic rates. Objective: To examine the rates of overweight and obesity in children with SCD compared to state and national norms and to assess the correlation between Hb and weight status. Methods: We conducted a retrospective chart review of patients with SCD between the ages of 2-19 years from October 2013 until April 2019. Data were collected from the most recent clinic visit and Body Mass Index (BMI) percentiles were calculated using Center for Disease Control growth charts. Mississippi and national weight status estimates for youth 10-17 years were obtained from the 2016-2017 National Survey of Children's Health. Results: Data were available for 787 patients. For children 10-17 years ($n = 480$), 24.5% of patients were overweight/obese compared to Mississippi and national rates, 39.2% and 31%, respectively. The prevalence of 10-17 year olds who were overweight (12.7%) was not significantly different from Mississippi (13.1%) or national (15.2%) ($p = 0.13$). Hb were different among patients who were underweight (8.80g/dL), normal weight (9.2g/dL), and overweight/obese (10.5g/dL) ($p < 0.001$). Conclusions: Children with SCD in Mississippi have similar rates of overweight compared to state and national norms and have higher Hb than patients with SCD who are normal weight/underweight. The impact of increased BMI in SCD is unknown and additional longitudinal studies are needed.

Introduction

Sickle cell disease (SCD) is the most common genetic disorder present in the United States, with about 1 in 13 African Americans being born with sickle cell trait and approximately 100,000 individuals currently living with disease. The state of Mississippi has the highest incidence rate of SCD in the United States(1). SCD is a life-limiting genetic condition that results in acute vaso-occlusive pain episodes, organ damage, stroke, and cardiovascular disease (2, 3).(5) Due to the chronic hemolysis [lysing of red blood cells (RBCs)] that occurs with sickle cell disease, patients with SCD have traditionally had a high basal metabolic rate and increased energy consumption (measured by resting energy expenditure) resulting from rapid production of new RBCs(3). Therefore, SCD has historically been characterized by poor growth, short stature, and patients being underweight to normal weight.

More recently, a retrospective chart review from 6 institutions in New England reported nearly one-quarter of children and adolescents with SCD are overweight or obese(4). This study found that the primary risk factor for children and adolescents with SCD being overweight/obese was increased baseline Hemoglobin levels (Hb), with a 36% increased odds of being overweight/obese for each 1g/dL increase in baseline Hb.

One possible explanation for this shift in weight status for children and adolescents with SCD is improved medical management. For instance, the use of chronic transfusion therapy and hydroxyurea medication have both been shown to increase children's z-scores for height, weight and BMI over 24 months compared to those children not on treatment(5, 6). These treatments increase hemoglobin level, reduce RBC turnover and reticulocytosis, and is thought to reduce the metabolic state and increased energy consumption that occurs in untreated SCD allowing for an increase in BMI.

Morbidity and mortality in SCD historically has been high due to complications of chronic hemolytic anemia, vaso-occlusion and impaired immune function. The mortality rate for children with SCD has improved in recent years due to comprehensive care, infection prophylaxis with penicillin and vaccination and the use of transcranial Doppler (TCD) to screen for stroke risk(7). As treatment continues to improve and mortality continues to decrease, an increase in BMI in SCD may emerge as a new risk factor for morbidity in this population. The consequences of overweight and obesity in children with SCD is currently unknown although it is thought to exacerbate comorbid conditions including obstructive sleep apnea, asthma and avascular necrosis(8). Systemic hypertension is an obesity-related complication which, has been associated with increased risk of stroke and death in patients with SCD(9). Adult studies have also demonstrated an increasing trend in BMI and a similar burden of type II diabetes among adult patients with SCD compared to African Americans without SCD. Specifically, adult patients with SCD have higher incidence of nephropathy, neuropathy and stroke(10).

The primary purpose of this study was to determine the prevalence of overweight and obesity in a pediatric population with SCD in Mississippi, compared to state and national rates of overweight and obesity. We hypothesized that rates of obesity in children with SCD in Mississippi would be similar to state and national rates. We further examined demographic (age, gender, insurance as proxy for socioeconomic status), baseline disease (genotype, hemoglobin level, hematocrit, absolute reticulocyte count), disease complications (acute chest syndrome, stroke, avascular necrosis), and treatment variables (hydroxyurea, chronic transfusion) as predictors of overweight/obesity in this sample.

Methods

Data Collection

We conducted a retrospective chart review of patients diagnosed with sickle cell disease (HbSS, HbSC, HbSβ^+, or HbSβ°),between the ages of 2-19 years, who were seen at an outpatient Pediatric Hematology appointment at the University of Mississippi Medical Center (UMMC) from October 2013 until April 2019. Data were collected from the UMMC electronic health record. The most recent clinic visit was utilized for individuals with multiple outpatient visits. Chronic transfusion treatment, prescribed medication, and disease complication (history of acute chest syndrome, stroke, and avascular necrosis) variables were extracted from the EHR by hand, while all other variables were abstracted by a computer-generated report.

Demographics and Medical Variables

Demographic information including age at the most recent clinic visit, gender, ethnicity and type of insurance as proxy for socioeconomic status were extracted from the EHR. Baseline disease information included the genotype, baseline hemoglobin level, hematocrit and absolute reticulocyte count. Treatment variables included both hydroxyurea and chronic transfusion therapy. Hydroxyurea was included as a treatment if the medication had been prescribed to the patient although compliance of the medication was not factored. Chronic transfusion therapy was for patients with history of stroke, abnormal TCD, severe acute chest syndrome or severe pain. Disease complications such as acute chest syndrome, stroke and avascular necrosis were extracted by hand from the medical record.

Overweight/Obesity

Height (cm) and weight (kg) were extracted from the most recent clinic visit and used to calculate body mass index (BMI) and BMI percentiles using age and gender Center for Disease Control growth charts(11). Underweight, overweight and obesity weight status category were the primary outcome and were defined as

a BMI percentile of $<5^{th}$, $>85^{th}$and $>95^{th}$ percentile, respectively. BMI z-scores were also calculated based on age and gender norms (12).

Mississippi state and national weight status estimates for youth 10-17 years were obtained from the 2016-2017 National Survey of Children's Health (NSCH) with a data agreement between the study authors and the Data Resource Center and the Child and Adolescent Health Measurement Initiative (CAHMI). The NSCH was a nationally representative survey, sent via mail and email to randomly selected addresses, on the health and well-being of youth aged 0 to 17 years living in the United States. This was both a population-based and cross-sectional study, which included 37,409 youth. Parent-reported height and weight data were utilized to calculate Body Mass Index (BMI). Weighted estimates were calculated for this study using the SPSS v26 Complex Samples module (IBM SPSS, 2019) (13).

Statistical Analysis Plan

Numerical summaries for continuous demographic variables were reported with medians and IQR (interquartile range, 75% th - 25% th) and frequencies and percentages for categorical variables. Demographic, baseline disease, disease complication, and treatment variables between SCD genotype groups and weight status groups were compared using Chi-square tests or Fisher's exact test with Monte Carlo estimates for categorical variables and Kruskal–Wallis tests for continuous variables. The weight status of patients with SCD at UMMC, who were 10-17 years, was compared to state and national proportions of 10-17 year olds from the 2016-2017 National Survey of Children's Health using two-sample tests of proportion. Variables that were found to be related to weight status ($p < 0.10$) were identified as potential risk factors. To examine how these potential risk factors may affect the relationship between SCD genotype and weight status, multiple logistic regressions models were conducted with risk factor groups accounted for sequentially. The odds ratio (OR) and 95% confidence intervals for genotype [HbSS/HbSβ° (ref) vs HbSC/ HbSβ^{+}] were reported for each model. All statistical analyses were performed using Stata 16.0.

Results

Patient Characteristics

Data were collected on 781 pediatric patients with SCD age 2 to 19 years, 462 (58.7%) with genotype HbSS/HbSβ° and 319 (41.3%) with genotype HbSC/ HbSβ^{+}. Mean age was 10.8 years, 99% African American, and 82% had public insurance. There was no difference in the male to female ratio and no difference in age among the groups. Table 1 presents participant characteristics.

Patients with HbSS+/HbSβ° had more acute chest syndrome, stroke, avascular necrosis, and more of these patients were on treatment with hydroxyurea or on chronic transfusion therapy. Patients with SCD HbSC/HbSβ^{+} had a higher median BMI percentile (71%) verses patients with SCD HbSS/HbSβ°, who had a BMI percentile of 48.5%. There was a statistically significant differences in the hemoglobin levels and absolute reticulocyte count among the genotype groups. Patients with SCD HbSC/ HbSβ^{+} had a median hemoglobin level of 10.9 g/dL and absolute reticulocyte count of 146, versus patients with SCD HbSS/HbSβ° who had a median hemoglobin level of 8.5 g/dL and absolute reticulocyte count of 306.

Weight Status

The weight status prevalence among pediatric patients with SCD at UMMC, age 10-17, is compared to state and national prevalence in Table 2. The prevalence of underweight pediatric patients with SCD (4.4%) was similar to the prevalence in Mississippi (4.3%, $p = 0.96$) and across the United States (6.2%, $p = 0.09$). The prevalence of normal weight in pediatric patients with SCD was higher (74%) compared to state and national prevalence (56% and 62.8%, respectively). The prevalence of overweight in pediatric patients with SCD (12.7%) was similar to state and national prevalence (13.1% and 15.2%, respectively). Finally, the prevalence of obesity in pediatric patients with SCD in Mississippi (9.0%) was significantly lower than the state (26.1%, $p < 0.001$) and national (15.8%, $p< 0.001$) prevalence.

Risk Factors

Table 3 shows demographic, baseline disease, disease complication, and treatment variable differences between the three weight status groups: underweight, normal weight, and overweight/obese. There were 193 (24.5%) pediatric patients with SCD identified as overweight or obese. Both hemoglobin ($p<0.001$) and absolute reticulocyte count ($p<0.001$) were significantly different values among the three weight status groups, with hemoglobin increasing and absolute reticulocyte count decreasing with increasing weight status.

TABLE 4 shows ORs for potential risk factors for overweight/obesity status in pediatric patients with SCD. Among patients with SCD, those with SC/Sβ^+ genotype were 2.59 times more likely to be obese/overweight as patients with the SCD HbSS/HbSβ° [OR: 2.59 (95%CI: 1.85, 3.61)], before adjusting for other potential risk factors. After accounting other risk factors, patients with HbSC/HbSβ^+ genotype still had increased odds of being obese or overweight compared to patients with the HbSS/HbSβ° genotype [OR: 1.80 (95%CI: 1.09, 2.99)]. There was also increased risk of being overweight/obese with older age and with increasing hemoglobin levels [OR: 1.22 (95%CI: 1.05, 1.40) and OR: 1.29 (95%CI: 1.13, 1.47) respectively]

After accounting for hydroxyurea use in logistic regression analyses, the odds of being obese/overweight increased slightly, although not significant ($p = 0.23$). We conducted post-hoc analyses to investigate if hydroxyurea use moderated the relationship between obesity and hemoglobin in pediatric patients with HbSS/HbSβ+ genotypes only. However, we found no significant interactions between hydroxyurea and Hemoglobin [OR: 0.94 (95%CI: 0.69, 1.29), $p = 0.70$].

Discussion

To date this is the largest study looking at weight status in children and adolescence with SCD. Mississippi currently has the highest incidence of patients with sickle cell disease and also has the highest pediatric and adult obesity rates in the nation at 25.4% and 39.5% respectively(14, 15). In our sample, patients were more likely to be overweight/obese (24.5%) versus underweight (4.4%). Our sample of pediatric patients with SCD had a similar prevalence rate of overweight as both state and national prevalence rates. Additionally, the combined overweight/obesity rate for the current sample (24.5%) is comparable to other published national overweight/obesity rates ranging from 22-25% (15). Higher hemoglobin levels and lower absolute reticulocyte count were significantly associated with a higher BMI.

Historically, poor growth, short stature, and being underweight have been a concern in patients with SCD. Children with SCD are known to have higher resting energy expenditure compared to control children and this in part is associated with chronic anemia. Hemoglobin levels are highly correlated ($r = 0.7$) with resting energy expenditure(4, 16). Our current study found a significant relationship between increased hemoglobin levels and increased BMI which is consistent with past studies looking at improved growth in SCD. The Stroke Prevention Trial showed that children with SCD who were chronically transfused to maintain a hematocrit greater than 30% had significant improvement in height, weight and BMI z-scores such that after 2 years of treatment, they were of comparable size to their healthy peers(16). While we hypothesized that hydroxyruea and chronic transfusion therapy would be associated with increased BMI, current results did not support this hypothesis. These relationships may be too complex to capture in cross-sectional data, as patients on hydroxyruea and chronic transfusion therapy tend to have the most severe disease and medical compliance, or lack thereof, may impact results.

Overweight and obesity in otherwise healthy children is associated with medical complications such as hypertension, dyslipidemia, insulin resistance, dysglycemia, fatty liver disease and psychosocial complications (17). Metabolic syndrome, which includes: increased waist circumference, elevated triglycerides and fasting glucose and elevated blood pressure is a key-risk factor for cardiovascular disease(16). Prospective studies are needed that evaluate the consequence of overweight and obesity on the health of pediatric patients with SCD. It will be important to gauge the impact of elevated BMI on both morbidity and mortality in SCD as medical interventions continue to improve for SCD. This may ultimately impact guidelines for screening, as well as nutrition and exercise guidelines for these patients.

Although this study has the strength of having a large sample size ($N = 781$) and robust measurement of disease-related variables, several limitations warrant discussion. The primary limitation is being a ret-

rospective cross-sectional chart review study. This type of data has inherent limitations as it exists for clinical purposes and random error in the data must be assumed. Additionally, a causal relationship between increased hemoglobin and decreased absolute reticulocyte count with increased weight status cannot be concluded with retrospective data. Further, this sample is limited to pediatric patients with SCD in Mississippi. BMI is strongly associated with genetic and environmental factors such as individual and family diet and exercise patterns(18). While current study results are similar to Chawla et al., (2013), these results may not generalize to other pediatric patients with SCD across the United States.

Conclusion

The current study suggests that pediatric patients with SCD in Mississippi now have similar prevalence rates of being overweight as state and national norms, in contrast with historically being underweight to normal weight. Those patients who are overweight/obese have a higher median basal hemoglobin level than patients who are underweight or normal weight. Prospective research is needed to examine if modern treatments, including hydoxyurea and chronic transfusions, that increase basal hemoglobin level may contribute to this increased rate of being overweight/obese in children with SCD. The overall impact of increased BMI in these patients is unknown and additional studies in this area are needed.

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Data Availability Statement : The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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