

High body mass index in children with sickle cell disease: a retrospective single-centre audit

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ABSTRACT

Objective To assess the prevalence of high body mass index (BMI) in children with sickle cell disease and assess correlation between BMI and disease severity.

Design Retrospective chart review followed by statistical analysis.

Setting A single tertiary paediatric clinic in inner city London.

Patients All patients with sickle cell disease, including homozygous haemoglobin (HbSS) and compound heterozygous Hb (HbSC), age 2–18 years receiving clinical care at the centre, were included in the study.

Interventions Height and weight measurements, steady-state laboratory blood tests, hospital admission rates, adjunct therapy such as hydroxycarbamide or blood transfusions and obstructive sleep apnoea (OSA) data were obtained from the hospital electronic patient records.

Main outcome measures To study the prevalence of high BMI and to identify any correlation between BMI and disease severity.

Results 385 patients were included. 64 children (17%) were overweight or obese, of which a significantly higher number of children with HbSC were obese or overweight (23 out of 91, 25%) compared with those with HbSS (36 out of 273, 13%), $p < 0.001$. No correlation was found between high BMI and presence of OSA, and markers of disease severity such as admission rates, fetal haemoglobin or lactate dehydrogenase levels.

Conclusions High BMI did not correlate with disease severity in this cohort of patients with sickle cell disease. Obesity was more prevalent in females and those with HbSC. Further prospective studies are needed to determine long-term effects of BMI in disease severity and outcome.

INTRODUCTION

Sickle cell disease (SCD) is one of the most common clinically significant genetic disorder in England, affecting up to 1 in 300 live births in urban areas.¹ The most common and severe form of SCD, sickle cell anaemia, refers to homozygosity for the sickle haemoglobin (Hb), known as HbSS.² Two major pathophysiological processes of SCD, vaso-occlusion with ischaemia-reperfusion injury and chronic haemolytic anaemia, are driven by HbS polymerisation within erythrocytes.³

What is already known on this topic?

- ▶ Children with sickle cell disease (SCD), especially those with the homozygous disease, were historically underweight due to increased metabolic demand and frequent ill health.
- ▶ In the USA, increased frequency of childhood obesity within the general population is also reflected among patients with SCD.
- ▶ Obesity in SCD is not associated with disease severity.

What this study hopes to add?

- ▶ One in six children with sickle cell disease (SCD) in a large single-centre UK-based cohort were overweight or obese, while only 1 in 20 children with SCD were underweight.
- ▶ There was a trend for higher haemoglobin values in children who were overweight or obese compared with those with normal body mass index (BMI) centiles, even when corrected for age and hydroxyurea use and genotype, highlighting the need for further study in this area.
- ▶ Overweight or obese children did not have higher rates of hospitalisation compared with those with normal BMI.

Historically, it is well documented that children with SCD were underweight, particularly those with HbSS.⁴ Poor growth in children with SCD is complex and multiple factors are likely to contribute, including increased energy and nutrient requirements resulting from increased haemolysis and erythropoiesis, and elevated protein turnover.⁵

Obesity in the UK is increasing with recent figures suggesting that nearly one-third (31%) of boys and more than one in four girls (28%) aged between 2 and 15 years are overweight or obese.⁶ Although the increasing incidence is almost certainly due environmental factors, genetic factors also strongly affect susceptibility to obesity.⁷

Two reports in the USA found that 19%–22% of children with SCD were



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overweight or obese.^{8 9} Nutritional status and growth may have improved in SCD due to the increased use of SCD-directed therapies and lifestyle factors.⁹ Children in the Stroke Prevention Trial in Sickle Cell Anaemia who regularly received transfusions over 24 months demonstrated a significant improvement in z-scores for height, weight and body mass index (BMI).¹⁰ Hydroxycarbamide (HC), which was, until recently, the only drug licensed for the use in SCD, lowers resting energy expenditure, improving energy balance and growth.¹¹ Preventing obesity in children with SCD is vital as obesity is associated with obstructive sleep apnoea (OSA), which increases the risk of nocturnal hypoxia and vaso-occlusive episodes (VOEs).¹²

There is limited data assessing the prevalence of high BMI in children with SCD in the UK and the relationship between BMI and disease severity. One study in the USA demonstrated that there was a 36% increase in odds of being overweight or obese for each 1.0g/dl increase in baseline Hb levels.⁹ Another study failed to demonstrate an association between the extremes of BMI of patients and hospitalisation for VOE.⁸ The purpose of this study is to assess the prevalence of high BMI in an urban population of children with SCD in the UK and evaluate whether there is a correlation between BMI and disease severity.

METHODS

Data collection

A retrospective chart review was performed on patients aged 2–18 years with SCD who were registered to the National Haemoglobinopathy Register¹³ and attended a paediatric haematology outpatient clinic in a single tertiary hospital in inner city London, between April 2015 and April 2017. Patients transferred to other centres were excluded.

Clinical and laboratory data

All children are weighed and measured when they attend clinic by trained clinical staff using standard, calibrated equipment. BMI and BMI percentile documented from the most recent clinic visit were recorded. Age-specific and gender-specific definitions of BMI percentiles were used, based on the British 1990 growth reference charts, as recommended in England by the National Obesity Observatory.^{14 15} Overweight or high BMI was defined as ≥ 85 th percentile for age and gender (obese was defined as ≥ 95 th percentile for age and gender), while underweight or low BMI was defined as ≤ 5 th BMI percentile. Patients were assigned to one of three groups based on their age-dependent percentile: underweight, normal weight, overweight/obese as per well-established clinical classifications.¹⁶ Data were categorised in order to study the influence of obesity on disease severity.

Through retrospective chart review, markers of disease severity were recorded, including acute sickle cell-related accident and emergency (A&E) attendances and hospital admissions during the 24-month period. Elective

admissions were excluded. Patients were assigned to none, 1 or >1 A&E attendances and none, 1 or >1 hospital admissions. Other indices of disease severity were recorded, including Hb, reticulocyte count, lactate dehydrogenase (LDH) levels and fetal Hb (HbF) level from the most recent blood test. Hb was a mean of the last three steady-state results. The use of SCD-directed treatments during this period was recorded.

Statistical analysis

Association between BMI group and independent variables was examined by χ^2 test for categorical variables and independent samples t-test for continuous variables. Given the small number of low BMI subjects in this study ($n=20$), only normal and high BMI groups were compared for differences with respect to laboratory data. Given the difference in disease severity by genotype, HbSS and heterozygous Hb (HbSC) clinical and laboratory data were assessed separately.¹⁷ Linear multiple regression analysis was undertaken to predict the relationship of BMI centiles with independent variables such as laboratory markers of disease severity and use of HC. P values less than 0.05 were considered significant. All analyses were performed using the IBM SPSS Statistics, V.24 (IBM).

Ethical considerations

This study involved retrospective chart reviews and no identifiable patient data have been reported. Hence, this was classified as a clinical audit.

RESULTS

Patient population

Three hundred and eighty-five children and adolescents with SCD between ages 2 and 18 years were included in the study. Seventy-one per cent children ($n=273$) had HbSS and 24% children ($n=91$) had HbSC disease (table 1). Fifty-three per cent ($n=204$) were male. Twenty-eight per cent patients ($n=108$) were receiving HC therapy and 7% ($n=27$) chronic transfusions. Fifty-five patients (14%) had a clinical diagnosis of OSA.

In the whole cohort, 17% children ($n=64$) were overweight or obese. Of these, 33 children (9% of the whole cohort) were classified as overweight; with BMI on or between the 85th and 95th centile for age and gender, and 31 children (8% of the whole cohort), were classified as obese; with BMI greater than 95th centile for age and gender. Twenty children (5%) had a low BMI (≤ 5 th centile for age and gender) and 301 children (78%) had a normal BMI (table 2). Significantly more females had a high BMI (26%, $n=47$) than males (8%, $n=17$) ($p\leq 0.001$). Patients in the low BMI group were significantly more likely to be older than those in the normal BMI group. Significantly more patients with HbSC disease were overweight or obese (23 out of 91, 25%) than patients with HbSS (36 out of 273, 13%) ($p=0.006$). There was no

Table 1 Demographics of the study population

	No	Percentage
Sex		
Male	204	53.0
Female	181	47.1
Age group (years)		
0–4	78	20.3
5–9	133	34.5
10–14	104	27.0
15–18	70	18.2
Ethnic origin		
African	320	83.1
Caribbean	59	15.3
Other	6	1.6
Genotype		
Homozygous haemoglobin (HbSS)	273	70.9
HbSβ0	6	1.6
HbSβ+	15	3.9
Heterozygous haemoglobin	91	23.6
Hydroxycarbamide		
Yes	108 (104 HbSS)	28.1
No	277	71.9
Chronic transfusions		
Yes	27	7.0
No	358	93.0
Sleep apnoea		
Yes	55	14.3
No	330	85.7

significant difference between BMI group and ethnic origin, chronic transfusions and OSA.

BMI and HC therapy

Twenty-eight per cent patients with HbSS received HC therapy (n=104), see table 3. There was no significant difference between BMI group and HC treatment (p=0.47).

BMI, clinical and laboratory data

No significant difference in the number of A&E attendances or hospital admissions between the three BMI groups in patients with HbSS or HbSC disease (table 4).

The median Hb was significantly higher in the high BMI group (9.5 g/dl) compared with the normal BMI group (8.6 g/dl) for patients with HbSS (p<0.001) (table 5). Further analysis indicated that the association may persist even when corrected for age at visit, HbF percentage, use of HC and genotype (HbSS vs HbSC) (p=0.048), data not shown. Although the median absolute reticulocyte count and the median HbF percentage were significantly lower in the high BMI group compared with the normal BMI

Table 2 Baseline characteristics by BMI group

	BMI group (n=385)			P values
	Low	Normal	High	
Total, n (%)	20 (5.2)	301 (78.2)	64 (16.6)	
Sex, n (%)				
Male	12 (5.9)	175 (85.8)	17 (8.3)	<0.001
Female	8 (4.4)	126 (69.6)	47 (26.0)	
Age, years				
Median	12.8	10.1	10.7	0.005*
Range	3.7–18.3	2.0–18.9	2.0–18.4	
Ethnic origin, n (%)				
African	16 (5.0)	253 (79.1)	51 (15.9)	0.952
Caribbean	4 (6.8)	43 (72.9)	12 (20.3)	
Other	0 (0)	5 (83.3)	1 (16.7)	
Genotype, n (%)				
HbSS	17 (6.2)	220 (80.6)	36 (13.2)	0.006**
HbSβ0	0 (0)	5 (83.3)	1 (16.7)	
HbSβ+	2 (13.3)	9 (60.0)	4 (26.7)	
HbSC	1 (1.1)	67 (73.6)	23 (25.3)	
Chronic transfusions, n (%)				
Yes	1 (3.7)	21 (77.8)	5 (18.5)	0.910
No	19 (5.3)	280 (78.2)	59 (16.5)	
Sleep apnoea, n (%)				
Yes	1 (1.8)	45 (81.8)	9 (16.4)	0.493
No	19 (5.8)	268 (77.6)	59 (16.7)	

*P value represents results from t-test for low versus normal BMI group.

**P value of HbSS versus HbSC only.

BMI, body mass index; HbSC, heterozygous haemoglobin; HbSS, homozygous haemoglobin.

group, this correlation did not achieve significance when corrected for HC use. Additionally, there was no significant difference between BMI group and LDH level or for all laboratory markers of disease severity between low and normal BMI groups.

There was no significant difference for patients with HbSC disease between normal and high BMI groups and laboratory markers of disease severity.

Table 3 Hydroxycarbamide therapy by BMI group in patients with HbSS genotype

BMI group	Hydroxycarbamide therapy, n (%)		P values
	Yes (n=104)	No (n=169)	
Low (≤5th percentile)	6 (5.8)	11 (6.5)	0.477
Normal (6 th –84 th percentile)	81 (77.9)	139 (82.2)	
High (≥85th percentile)	17 (16.3)	19 (11.2)	

BMI, body mass index; HbSS, homozygous haemoglobin.

**Table 4** A&E attendances and hospital admissions by BMI group for a 2-year period from April 2015

	BMI group			P values*
	Low (n=17)	Normal (n=220)	High (n=36)	
Patients with HbSS (n=273)				
A&E attendances, %				
0	88.2	68.2	72.2	0.450
1	5.9	22.3	22.2	
>1	5.9	9.5	5.6	
Hospital admissions, %				
0	58.8	63.2	55.6	0.780
1	17.6	21.4	22.2	
>1	23.5	15.5	22.2	
Patients with HbSC (n=91)				
A&E attendances, %				
0	100.0	82.1	91.3	0.838
1	0	11.9	4.3	
>1	0	6.0	4.3	
Hospital admissions, %				
0	100.0	86.6	95.7	0.750
1	0	6.0	0	
>1	0	7.5	4.3	

Values may not sum to 100% as figures were rounded to 1 decimal place.

A&E, accident and emergency; BMI, body mass index; HbSC, heterozygous haemoglobin; HbSS, homozygous haemoglobin.

DISCUSSION

Seventeen per cent of children with SCD, including 25% of those with HbSC disease, in this single-centre cohort were overweight or obese. There was no association between BMI group and clinical disease severity, determined by the number of A&E attendances and hospital admissions.

The proportion of overweight or obese children with SCD noted in this London cohort is similar to that in two centres in the USA, where 19%–22% children were reported to be overweight or obese. However, it is noteworthy that fewer children with SCD are overweight or obese compared with all children across London, where 35%–40% children fall in these weight categories.^{8 9 18} This is understandable as multiple factors increase the demand for energy and nutrients in SCD.^{5 19} Females were more likely to be overweight or obese than males, similar to one other study,²⁰ but not another.⁹ A high BMI was more often associated with the HbSC genotype, consistent with other reports.^{8 9} It is also consistent with data demonstrating that growth in children with HbSC disease is not significantly different from that in normal children.²¹

It is of note that in our cohort, SCD is predominantly prevalent among individuals of African or Afro-Caribbean heritage. BMI centile charts used in this study were based on children of white ethnicity only,²² as this is

the recommended BMI reference source in England.¹⁴ Although it is likely that ethnic variation in BMI is prevalent in the UK, this may not be of relevance to the SCD population, as the vast majority of patients with SCD in the UK belong to ethnicities similar to that noted in our cohort.²³

It is known that HC can decrease the resting energy expenditure by 8%, by decreasing the severity of anaemia and increasing red cell survival, making more energy available for normal growth.^{11 24 25} A randomised study looking at the effect of growth in patients with HbSS receiving HC in the BABYHUG trial did not show any difference in growth parameters at study entry and exit.²⁶ However, that study involved infants only, and the duration of the study may not have been long enough to demonstrate the effect of HC on growth. The duration of SCD-directed treatment was not collected in this study and some patients may only be taking HC for a short period.

No correlation between BMI group and clinical markers of disease severity was found. The results are similar to a single centre, retrospective chart review of children with SCD from the USA where no association was found between extremes of BMI and frequency of hospitalisations for VOE.⁸ The study only used the first admission during the study period in data analysis and did not look at the total number of admissions. This may not represent the true severity of SCD.

Table 5 Laboratory data by BMI group for patients with HbSS and HbSC

	BMI group			P values*
	Low (n=17)	Normal (n=220)	High (n=36)	
Patients with HbSS(n=273)				
Hb, g/dl				
Median	8.2	8.6	9.5	<0.001
Range	7.0–10.2	6.3–13	7.2–12.6	
ARC, x10⁹/L				
Median	360.5	374.3	299.2	0.022
Range	111.3–483.5	105.5–852.0	100.0–609.6	
LDH, IU/L				
Median	517	566	496	0.053
Range	350–838	241–1263	236–883	
HbF, %				
Median	6.7	8.3	16.1	0.010
Range	1.1–21.6	0.5–31.8	1.1–33.7	
Patients with HbSC (n=91)				
Hb, g/dl				
Median	11.3	11.2	11	0.149
Range	–	8.7–12.8	10.3–14.5	
ARC, x10⁹/L				
Median	219.2	176.0	225.7	0.064
Range	–	40.3–371.5	110.7–294.6	
LDH, IU/L				
Median	392	344	328	0.104
Range	–	194–494	170–415	
HbF, %				
Median	–	2.25	6.1	0.255
Range	–	0.3–16.9	0.6–13.0	

*P value represents results from t-test for normal versus high BMI group.

ARC, absolute reticulocyte count; BMI, body mass index; HbF, fetal haemoglobin; HbSC, heterozygous haemoglobin; HbSS, homozygous haemoglobin; LDH, lactate dehydrogenase.

Hb levels demonstrated an association with high BMI in patients with HbSS compared with those with normal BMI even when corrected for HC use, genotype and HbF levels. This is an interesting finding and requires further study. One study found that for each 1.0 g/dL increase in baseline Hb, there was a 36% increase in odds of being overweight or obese.⁹ It could be hypothesised that less severe anaemia decreases the need for a hyperdynamic circulation, which reduces energy and nutrient demand, and could also be a marker of a less severe phenotype in general.¹⁹

No significant difference was found between BMI group and laboratory markers in patients with HbSC disease. Some haematological features of HbSC disease are more like those of a normal individual as there is less haemolysis, a milder anaemia and fewer reticulocytes.¹⁷

This study has some limitations. As it is retrospective, it is not possible to establish causation. Only data concerning attendances and admissions to our hospital were obtainable and it does not cover all potential A&E attendances or admissions. The patient sample is only representative of an urban population of children with SCD in the UK and will not be generalisable to all children with SCD. Duration of UK residency was not recorded, which could underestimate the prevalence of high BMI as children from low-income and middle-income countries are frequently underweight.⁴

Several studies have suggested that waist circumference and waist to height ratio are better determinants of obesity in children than BMI, but body fat measured by dual-energy X-ray absorptiometry (DEXA) is shown to be strongly correlated with BMI and weight to height

ratio, suggesting that either can be used when DEXA is not available.^{21–27} Despite the advantages of using BMI percentiles for age and gender, there are limitations of BMI. BMI is an imperfect tool to determine weight status because it does not distinguish between excess fat or lean muscle mass.²⁸ BMI may not be appropriate for young children because they grow at different rates and so weight to height ratio does not accurately represent whether they are overweight.²⁹

Longitudinal cohort studies monitoring BMI of children over time and markers of severity in SCD would produce greater evidence of the impact of a high BMI on disease severity. Preventing obesity is vital in SCD as OSA increases the risk of night time hypoxia and VOE.¹² Obesity is also associated with hypertension, which increases the risk of stroke and death in SCD.³⁰ Given that a significant proportion of children with SCD are overweight or obese and patients with SCD commonly have multiple nutrient deficiencies, creating the optimum nutrition and exercise regimen for children and adolescents with SCD is vital to assist them in maintaining a healthy BMI.³¹

CONCLUSION

The historical observation that children with SCD were underweight is no longer true, at least in high-income countries. Nearly one-sixth of children with SCD in this cohort were overweight or obese, with a high BMI more often associated with females and HbSC genotype. In this study, no association was found between BMI levels and several disease severity markers, including hospital admission rates. Further longitudinal prospective study looking at growth and BMI in children with SCD and its effect on disease severity and the effect of the use of sickle-directed therapies on BMI is needed.

Contributors SC designed the study. RH conducted the data collection and analysis. KG and DCR assisted in data analysis. All authors wrote and reviewed the manuscript.

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