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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 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 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. 17% children were overweight or obese, of which a significantly higher percentage of children with HbSC were obese or overweight (25%), compared to those with HbSS (13%), *P*=<0.001. The mean BMI for HbSS patients taking hydroxycarbamide was significantly higher (18.3kg/m^2) than those not (17.2kg/m^2) (*P*=0.003). Haemoglobin values were significantly higher in overweight or obese children, even when corrected for age, use of hydroxycarbamide and fetal haemoglobin (HbF) levels. No correlation was found between high BMI and presence of OSA, and markers of disease severity such as admission rates, HbF or lactate dehydrogenase levels.

Conclusions:

Fewer children with Sickle Cell Disease were overweight or obese compared to all children across London and high BMI did not correlate with disease severity. Longitudinal growth studies are important for providing weight management advice for patients with SCD.

Introduction

Sickle cell disease (SCD) is one of the commonest 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).

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 a third (31%) of boys and more than one in four girls (28%) aged between two and fifteen years are overweight or obese (6). Although the increasing incidence is almost certainly due environmental factors, genetic factors strongly affect susceptibility to obesity (7). At least 32 loci have been found by genome-wide association studies (GWAS) to be associated with adiposity levels and susceptibility to obesity (7). Analysis of the 32 loci showed that they only have a small effect on obesity susceptibility, with one paper estimating they account for 6-11% of genetic variation in BMI. (8) (9). The identification of further loci that influence obesity susceptibility may ultimately increase the understanding of obesity as a disorder and allow for personalised obesity therapy (7).

Two reports in the United States (US) found that 19-22% of children with SCD were overweight or obese (10) (11). Nutritional status and growth may have improved in SCD due to the increased use of SCD-directed therapies and lifestyle factors (11). Children in the Stroke Prevention Trial in Sickle Cell Anaemia (STOP) who regularly received transfusions over 24 months demonstrated a significant improvement in z-scores for height, weight and body mass index (BMI) (12). Hydroxycarbamide (HC), which was, until recently, the only drug licenced for the use in SCD, lowers resting energy expenditure, improving energy balance and growth (13). 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 (VOE) (14).

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 US demonstrated that there was a 36% increase in odds of being overweight or obese for each 10g/L increase in baseline Hb levels (11). Another study failed to demonstrate an association between the extremes of BMI of patients and hospitalisation for VOE (10). 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 to 18 years with SCD who were registered to the National Haemoglobinopathy Register (15) and attended a paediatric haematology outpatient clinic in a single tertiary hospital in inner city London, between April 2015 and April 2017. Only patients with the genotypes HbSS, HbSβ^0, HbSβ^+ or HbSC were included. 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 and gender specific definitions of BMI percentiles were used, based on the British 1990 growth reference charts (16). Overweight, or high BMI, was defined as ≥85th percentile for age and gender, whilst underweight, or low BMI, was defined as ≤5th BMI percentile. Patients were assigned to one of three groups based on their percentile: low, normal and high BMI.

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 were examined by chi-squared 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 HbSC clinical and laboratory data were assessed separately (17). 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, version 24 (IBM., Armonk, NY).

Ethical considerations

This study involved retrospective chart reviews and no identifiable patient data have been reported. Hence this was classified as a clinical audit and no formal ethical approval was sought for this study.

Results

Patient population

385 children and adolescents with SCD between ages 2-18 years were included in the study. 71% and 24% of patients had HbSS and HbSC disease respectively (Table 1). 53 % of the sample were male. 28% of patients were receiving HC therapy and 7% chronic transfusions. 14% of patients had a clinical diagnosis of obstructive sleep apnoea (OSA).

Seventeen percent of patients were overweight or obese, 78% had a normal BMI and 5% had a low BMI (Table 2). Significantly more females had a high BMI (26%) than males (8%) (*P*=<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 (25%) than HbSS patients (13%) (*P*=0.006). There was no significant difference between BMI group and ethnic origin, chronic transfusions and OSA.

BMI and hydroxycarbamide therapy

104 HbSS patients received HC therapy (38%), see Table 3. There was no significant difference between BMI group and HC treatment (*P*=0.477). The mean BMI for HbSS patients taking HC was significantly higher (18.3kg/m^2) than those not taking HC (17.2kg/m^2) (*P*=0.003).

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 5).

The median Hb was significantly higher in the high BMI group (95g/L) compared to the normal BMI group (86g/L) for HbSS patients (*P*=<0.001). This correlation persisted even when corrected for age at visit, Hb F percentage, use of HC and genotype (HbSS vs HbSC) (*P*=0.048), data not shown. Although the median absolute reticulocyte count (ARC) and the median HbF % were significantly lower in the high BMI group compared to the normal BMI 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.

Discussion

17% 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 association between BMI and haemoglobin values persisted even when corrected for the use of HC, genotype and HbF levels.

There were fewer overweight or obese children with SCD in this study compared to the US (19-22%) and compared to all children across London, with 40% being overweight or obese (10) (11) (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 (11). A high BMI was more often associated with the HbSC genotype, consistent with other reports (10) (11). It is also consistent with data demonstrating that growth in children with HbSC disease is not significantly different from that in normal children (26).

The mean BMI in HbSS patients taking hydroxycarbamide (HC) was significantly higher than those who were not. This supports the data suggesting 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 (13) (21) (22). A randomised study looking at the effect of growth in HbSS patients receiving HC in the BABYHUG trial did not show any difference in growth parameters at study entry and exit (23). 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. Potentially some of the beneficial effects of taking HC might be off-set by the increased numbers of obese and overweight patients. 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 US where no association was found between extremes of BMI and frequency of hospitalisations for VOE (10). 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.

HbSS patients in the high BMI group had a significantly higher Hb than those with a normal BMI, even when corrected for HC use, genotype and HbF levels. Another study found that for each 10g/L increase in baseline Hb, there was a 36% in increase in odds of being overweight or obese (11). A less severe anaemia decreases the need for a hyperdynamic circulation, which reduces energy and nutrient demand, and may 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. This could be because fewer HbSC patients are on HC so are not receiving the benefits of an increased Hb and HbF% and a lower ARC. 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 difficult 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. Immigration status was not recorded, which could underestimate the prevalence of a high BMI as children from developing 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 (24) (25). 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 (26). 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 (27).

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. Looking greater at genetic influences on obesity will help identify those who are at a greater risk of a high BMI and allow for personalised obesity therapy. Preventing obesity is vital in SCD as OSA increases the risk of night time hypoxia and VOE (14). Obesity is also associated with hypertension, which increases the risk of stroke and death in SCD (28) . 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 (29).

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. The mean BMI of HbSS patients taking HC was significantly higher than those not taking it. This association of HC therapy and higher BMI in children with HbSS has been demonstrated for the first time. In this study, no association was found between BMI levels and several disease severity markers, including hospital admission rates. Further research into the genetic influence on obesity and assessing the optimum nutrition and exercise regimen is essential to help children with SCD maintain a healthy BMI.

What is already known in this topic

Children with sickle cell disease (SCD), especially those with the homozygous disease HbSS 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 SCD patients. This may partly reflect improved uptake of sickle-directed therapies.

Obesity in SCD is not associated with disease severity.

What this study adds

The historical observation that children with SCD were underweight is no longer true, at least in high-income countries. One in six children with SCD in a large single-centre UK- based cohort were overweight or obese, whilst only one in 20 children with SCD were underweight.

Higher BMI was more prevalent in those with HbSC genotype than those with HbSS genotype. Those on hydroxycarbamide had significantly higher BMI than those who were not.

Overweight or obese children did not have higher rates of hospitalisation compared to those with normal BMI. However, haemoglobin levels positively correlated with BMI.

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Tables

TABLE 1 – Demographics of the study population

	Number	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		
HbSS	273	70.9
HbSβ0	6	1.6
HbSβ+	15	3.9
HbSC	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

TABLE 2 – Baseline characteristics by BMI group

	BMI group (n=385)			P value
	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)	
NOTE: *P value represents results from T-test for low vs. normal BMI group **P value of HbSS vs HbSC only				

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

BMI group	Hydroxycarbamide therapy, n(%)		P value
	Yes (n=104)	No (n=169)	
Low	6 (5.8)	11 (6.5)	0.477
Normal	81 (77.9)	139 (82.2)	
High	17 (16.3)	19 (11.2)	
Mean BMI (SD)	18.3 (3.6)	17.2 (2.8)	0.003

Abbreviations: BMI, body mass index

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

	BMI group			P value
HbSS patients (n=273)				
	Low (n=17)	**Normal (n=220)**	**High (n=36)**	
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	
HbSC patients (n=91)				
	Low (n=1)	**Normal (n=67)**	**High (n=23)**	
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 Abbreviations: BMI, body mass index; A&E, accident and emergency				

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

	BMI group			P value*
HbSS patients (n=273)				
	Low (n=17)	**Normal (n=220)**	**High (n=36)**	
Hb, g/L				
Median	82.0	85.7	95.3	<0.001**
Range	69.7-101.7	63.0-129.7	71.7-126.0	
ARC, $x10^9$/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	
HbSC patients (n=91)				
	Low (n=1)	**Normal (n=67)**	**High (n=23)**	
Hb, g/L				
Median	112.5	111.7	110.4	0.149
Range	-	87.0-127.7	102.7-144.7	
ARC, $x10^9$/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 vs. high BMI group.
** Using a linear regression model, BMI centile correlated significantly with Hb only (independent variable, *P*=0.048), but not with ARC, HbF and use of HC therapy.

Abbreviations: ARC, absolute reticulocyte count. LDH, lactate dehydrogenase. BMI, body mass index

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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 (Hb)SS and compound heterozygous 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 to 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 (HbF) 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 commonest 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).

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 a third (31%) of boys and more than one in four girls (28%) aged between two and fifteen 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 United States (US) found that 19-22% of children with SCD were 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 (STOP) 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 licenced 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 (VOE) (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 US demonstrated that there was a 36% increase in odds of being overweight or obese for each 10g/L 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 to 18 years with SCD who were registered to the National Haemoglobinopathy Register (13) 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 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 ≥85th percentile for age and gender (obese was defined as ≥95th percentile for age and gender), whilst underweight, or low BMI, was defined as ≤5th 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 were examined by chi-squared 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 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, version 24 (IBM., Armonk, NY).

Ethical considerations

This study involved retrospective chart reviews and no identifiable patient data have been reported. Hence this was classified as a clinical audit and no formal ethical approval was sought for this study.

Results

Patient population

385 children and adolescents with SCD between ages 2-18 years were included in the study. 71% children (n=273) had HbSS and 24% children (n=91) had HbSC disease (Table 1). 53% (n=204) were male. 28% patients (n=108) were receiving HC therapy and 7% (n=27) chronic transfusions. 55 patients (14%) had a clinical diagnosis of obstructive sleep apnoea (OSA).

TABLE 1 – Demographics of the study population

	Number	Percentage
Sex		
Male		
Female		
Age group (years)		
0-4		
5 9		
10 14		
15-18		
Ethnic origin		
African		
Caribbean		
Other		
Genotype		
HbSS		
HbSβ0		
HbSβ+		
HbSC		
Hydroxycarbamide		
Yes		
No		
Chronic transfusions		
Yes		
No		
Sleep apnoea		
Yes		
No		

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 (≤5th centile for age and gender) and 301 one children (78%) had a normal BMI (Table 2). Significantly more females

had a high BMI (26%, n=47) than males (8%, n=17) (*P*=<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 HbSS patients (36 out of 273,13%) (*P*=0.006). There was no significant difference between BMI group and ethnic origin, chronic transfusions and OSA.

TABLE 2 – Baseline characteristics by BMI group

[illegible]	BMI group (n=385)			P value
[illegible]	Low	Normal	High	
[illegible]	[illegible]	[illegible]	[illegible]	
[illegible]				
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	
[illegible]				
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	
[illegible]				
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	
[illegible]	[illegible]	[illegible]	[illegible]	
[illegible]				
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
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[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	
[illegible]				
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	
[illegible]				

BMI and hydroxycarbamide therapy

38% HbSS patients received HC therapy (n=104), see Table 3. There was no significant difference between BMI group and HC treatment (*P*=0.47).

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

BMI group	Hydroxycarbamide therapy, n(%)		P value
	Yes (n=104)	No (n=169)	
Low (≤ 5th Percentile)	6 (5.8)	11 (6.5)	0.477
Normal (6th-84th percentile)	81 (77.9)	139 (82.2)	
High (≥ 85th percentile)	17 (16.3)	19 (11.2)	
Abbreviations: BMI, body mass index			

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).

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

	BMI group			P value
HbSS patients (n=273)				
	Low (n=17)	**Normal (n=220)**	**High (n=36)**	
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	
HbSC patients (n=91)				
	Low (n=1)	**Normal (n=67)**	**High (n=23)**	
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 Abbreviations: BMI, body mass index; A&E, accident and emergency				

The median Hb was significantly higher in the high BMI group (95g/L) compared to the normal BMI group (86g/L) for HbSS patients (*P*=<0.001). (Table 5). Further analysis indicated that the association may persist even when corrected for age at visit, Hb F percentage, use of HC and genotype (HbSS vs HbSC) (*P*=0.048), data not shown. Although the median absolute reticulocyte count (ARC) and the median HbF % were significantly lower in the high BMI group compared to the normal BMI 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 5 – Laboratory data by BMI group for patients with HbSS and HbSC

	BMI group			P value*
HbSS patients (n=273)				
	Low (n=17)	**Normal (n=220)**	**High (n=36)**	
Hb, g/L				
Median	82.0	85.7	95.3	<0.001
Range	69.7-101.7	63.0-129.7	71.7-126.0	
ARC, $x10^9$/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	
HbSC patients (n=91)				
	Low (n=1)	**Normal (n=67)**	**High (n=23)**	
Hb, g/L				
Median	112.5	111.7	110.4	0.149
Range	-	87.0-127.7	102.7-144.7	
ARC, $x10^9$/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 vs. high BMI group.				
Abbreviations: ARC, absolute reticulocyte count. LDH, lactate dehydrogenase. BMI, body mass index				

Discussion

17% 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 US, 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 to 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 (26).

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 (21), 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 SCD patients in the UK belong to ethnicities similar to that noted in our cohort (22).

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) (23) (24). A randomised study looking at the effect of growth in HbSS patients receiving HC in the BABYHUG trial did not show any difference in growth parameters at study entry and exit (25). 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 US 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.

Hb levels demonstrated an association with high BMI in HbSS patients compared to 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 10g/L increase in baseline Hb, there was a 36% in 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 developing 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 (26) (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.

Competing interests

The authors declare no competing interests.

Contributorship Statement

SC planned and designed the study. RH conducted the data collection and analysis. DR and KG assisted in data analysis and interpretation. All authors reviewed and edited the manuscript.

What is already known in this topic

Children with sickle cell disease (SCD), especially those with the homozygous disease HbSS 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 SCD patients.

Obesity in SCD is not associated with disease severity.

What this study adds

One in six children with SCD in a large single-centre UK- based cohort were overweight or obese, whilst only one in 20 children with SCD were underweight.

There was a trend for higher haemoglobin values in children who were overweight or obese compared to those with normal 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 to those with normal BMI.

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