Muscle Strength, Power, and Torque Deficits in Children With Type SS Sickle Cell Disease

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Summary: In African-American children aged 5 to 17 years with and without type SS sickle cell disease (SCD-SS), dominant hand maximal handgrip strength, peak power, and plantar flexion isometric maximal voluntary contraction (MVC) torque were compared with adjustments for body size and composition. Children with SCD-SS (n = 21; age, 11 ± 1 y) compared with healthy control children (n = 23; 10 ± 1 y) did not differ by age, sex, or maturation stage, but had significantly lower *Z* scores for height, weight, body mass index, arm circumference, upper arm muscle area, and lean mass-for-height. Children with SCD-SS had significantly lower unadjusted handgrip strength (16 ± 2 vs. 23 ± 2 kg, $P < 0.01$), peak power (1054 ± 107 vs. 1488 ± 169 W, $P < 0.04$) and MVC torques at 2 angles (10 degrees: 27 ± 3 vs. 42 ± 5 Nm; 20 degrees: 21 ± 3 vs. 34 ± 4 Nm; all $P < 0.05$). Performance decrements persisted when handgrip strength was adjusted for lean body mass and fat mass explaining 66% of the variance; peak power adjusted for age, lean body mass, fat mass, and height explaining 91% of the variance; and the highest MVC torque (10-degree angle) adjusted for left leg length, lean mass-for-height, and fat mass-for-height *Z* scores explaining 65% of the variance. This suggests additional factors contribute to the attenuated anaerobic performance.

Key Words: pediatrics, muscle function, Biodex, sickle cell disease, muscle torque

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Throughout childhood, developing adequate muscle function is important for overall health, play activity and for rapid movement in emergency situations. Activities of daily living often require repeated bouts of anaerobic activity such as climbing the stairs or sprinting to catch a person or object. In addition, children at play frequently engage in short bursts of high-intensity exercise. Therefore, anaerobic activity patterns are of practical importance to a child's daily life.

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Previously, maximal muscle strength (by handgrip dynamometer) and peak power (by force plate) adjusted for body size and composition deficits were shown to be attenuated in children with type SS sickle cell disease (SCD-SS) compared with healthy African-American children.[1] However, no study in this population has investigated if these muscle performance deficits persist using a more functional measure, muscle torque, defined as force applied over a distance causing rotation about a fulcrum. As a foundation of human movement, measurement of muscle torque provides an integrated assessment, as almost all movement generates torque to varying degrees. In addition, in the current SCD clinical care environment, where the population of people with SCD may be upwards of 100,000 in the United States,[2] hydroxyurea is considered a standard of care treatment and is prescribed at a young age. It is unclear if hydroxyurea use or other changes in treatment over the last decade may have reversed these body size and muscle performance deficits.

The purpose of this study was to compare dominant hand maximum handgrip strength, peak power and plantar flexion isometric maximal voluntary contraction (MVC) torque, adjusted for body size and composition, in a contemporary sample of 5- to-17-year-old African-American children with and without SCD-SS. It was hypothesized that despite introducing hydroxyurea therapy at a younger age, children with SCD-SS have significantly reduced muscle strength, peak power, and plantar flexor MVC torques after adjustment for confounding variables such as body size and composition compared with healthy children.

METHODS

Subjects

This was a secondary analysis of a randomized trial and the primary outcome and methods have been previously reported in detail.[3] Briefly, African-American children aged 5 to 17 years with and without SCD-SS were recruited for a vitamin D supplementation study. The baseline data (before vitamin D supplementation) were used for this analysis. Children with SCD-SS were recruited from the Comprehensive Sickle Cell Center at the Children's Hospital of Philadelphia (CHOP). Healthy subjects were recruited from the CHOP network of primary care centers and the greater Philadelphia region. Exclusion criteria for both groups included: participation in another study impacting 25 hydroxyvitamin D; pregnant or lactating female individuals; other chronic conditions or use of medications affecting growth, dietary intake, or nutritional status; use of vitamin D to treat vitamin D deficiency; and baseline elevated serum calcium concentration. Subjects taking supplements containing vitamin D were not eligible. Those willing to

discontinue supplementation with approval of their medical provider were eligible after a 2-month washout period. Additional exclusion criterion for subjects with SCD were chronic transfusion therapy and for healthy subjects were body mass index (BMI) > 85th percentile for age and sex.[4]

This protocol was approved by the Institutional Review Board at CHOP. Written informed consent was obtained from parents/legal guardians of subjects below 18 years of age. Verbal assent was obtained from subjects 6 years to below 18 years of age.

Anthropometry and Pubertal Status

Anthropometric measurements were obtained in triplicate per standardized techniques[5] and the mean used for analysis. BMI was calculated (kg/m^2) from weight using a digital scale (Scaletronix, White Plains, NY) and standing height using a stadiometer (Holtain, Crymych, UK). Weight, height, and BMI were compared with reference standards to generate age-specific and sex-specific Z scores,[4] which is a measure of how many SDs below or above the population mean a measurement is located. Sixty-eight percent of normally distributed data are within one SD of the mean (between −1 and 1), 95% are within 2 SDs, and 99.7% are within 3 SD units of the mean. Skinfold thickness was measured at the triceps and subscapular sites with a skinfold caliper (Holtain) to estimate subcutaneous fat stores using prediction equations adapted for children and adolescents.[6,7] Midupper arm circumference and triceps skinfold thickness measures were used to calculate upper arm muscle area (UAMA) and upper arm fat area.[8] These areas were compared with reference data from the National Center for Health Statistics to generate the Z scores.[9] Total body fat and lean body mass (LBM) were measured using whole body dual energy x-ray absorptiometry (DXA; Delphi A, Hologic Inc., Bedford, MA) and compared with the Reference Project on Skeletal Development in Children data to generate race-specific and sex-specific DXA Z scores for LBM (LBM-for-height) and fat mass relative to height.[10] At baseline, pubertal status according to the criteria of Tanner[11] was determined using a validated self-assessment questionnaire.[12] Children were categorized into 3 groups for before to early puberty (Tanner stages 1 or 2), midpuberty (stage 3), or late puberty (stages 4 or 5).

Biochemistry and Hematology

Serum 25 hydroxyvitamin D was determined using liquid chromatography tandem mass spectrometry (Clinical Laboratory, CHOP) with intra-assay and interassay coefficients of variation below 7%. Hematologic status was assessed by complete blood count (hemoglobin, hematocrit, mean corpuscular hemoglobin [MCH], MCH concentration, mean corpuscular volume, and red blood cell distribution width) for all subjects and fetal hemoglobin was assessed in SCD-SS only according to standardized techniques. Serum high-sensitivity C-reactive protein was assessed in all subjects as an indicator of inflammatory status. Subjects with SCD-SS were categorized as receiving or not receiving hydroxyurea therapy during the study.

Muscle Performance

All subjects completed a 5-minute warm-up period of treadmill walking at a comfortable self-selected speed at 0% grade. Next, maximal handgrip strength of the right and left hand was measured in kilograms with a handgrip dynamometer (Takei Scientific Instruments Co. Ltd, Tokyo, Japan). Hand dominance was determined by asking which hand was used to hold a pencil. The participants stood upright with the shoulder adducted holding the dynamometer, not touching the trunk. The handle was adjusted to the hand size of the child and no extraneous body movement was allowed during testing. For each hand, 3 maximal effort trials lasting 4-seconds to 5-seconds interspersed with 60-second rests were carried out (verbal encouragement provided) and the highest dominant hand value was retained for analysis.

Peak power in watts was calculated from the force-time curve and velocity of the center of mass during a maximal vertical squat jump using a Kistler Quattro Jump Portable Force Plate System (Model 9290AD; Kistler Instrument Corporation, Amherst, NY). Participants completed 3 warm-ups followed by 3 maximal vertical jumps from an initial static squat position with knees at 90 degrees flexion and arms akimbo. The highest value was used for analysis.[13,14]

Muscle torque was assessed using the Biodex Multi-Joint System 3 Pro (Biodex Medical Systems Inc., Shirley, NY). High intrarater (0.97 to 0.99) and interrater (0.93 to 0.96) intraclass correlation coefficients have been reported for this method testing various body joints.[15] Before testing each subject was familiarized with the test procedures. Plantar flexion isometric MVC torques of the left ankle were measured in triplicate at each of 4 angles (−10, 0, 10, and 20 degrees) and the highest value in Newton meters recorded for dorsiflexion and plantar flexion at each angle.

Statistical Analyses

All variables were tested for normality, and nonparametric tests were used as appropriate. Group differences were determined by using a the Student t test or the Wilcoxon rank-sum test for continuous variables and the Fisher exact or χ^2 test for categorical variables. To assess potential group differences in muscle performance adjusted for age, and body size and composition, multivariate regression models were constructed using a multistage approach. Variables related to age, sex, body size, body composition, vitamin D, hematology and inflammatory status were explored, as was whether using or not prescribed hydroxyurea therapy. Selection of variables for final models was based on statistical significance, maximum R^2 values, and distribution of residuals. All statistical analyses were performed by using STATA 14.0 (Stata Corp, College Station, TX). Results were considered significant at $P < 0.05$, and data presented as mean ± SD.

RESULTS

Characteristics of subjects are presented in Table 1. Twenty-one children with SCD-SS and 23 healthy control children did not differ by age, sex, or maturation stage. Children with SCD-SS compared with healthy controls had significantly lower Z scores (all $P < 0.05$) for height, weight, BMI, arm circumference, UAMA, and whole body LBM-for-height. Hematocrit and hemoglobin were significantly lower and high-sensitivity C-reactive protein, MCH, mean corpuscular volume and red blood cell distribution width were significantly higher in children with SCD-SS versus healthy control children.

For those treated versus not treated with hydroxyurea therapy in the SCD-SS group, although there were no significant differences (all $P > 0.05$) in age (11 ± 4 vs. 11 ± 4), LBM-for-height Z score (−1.6 ± 1.2 vs. −2.1 ± 0.8), or fat

TABLE 1. Subject Characteristics

	SCD-SS	Controls
N	21	23
Age (y)	11 ± 4	10 ± 4
Sex (n)		
Male	9	13
Female	12	10
Tanner (n)		
1 or 2	14	13
3	3	5
4 or 5	4	5
Height *Z* score	−0.5 ± 1.2	0.4 ± 1.0*
Weight *Z* score	−0.7 ± 1.2	0.8 ± 1.1*
BMI *Z* score	−0.6 ± 1.1	0.7 ± 1.1*
Arm circumference *Z* score	−0.9 ± 1.1	0.8 ± 1.6*
UAMA *Z* score	−0.6 ± 1.2	1.0 ± 1.8*
LBM-for-height *Z* score	−1.9 ± 1.0	−0.9 ± 1.4*
Hematocrit (%)	25.9 ± 3.1	39.8 ± 3.1*
Hemoglobin (g/dL)	8.4 ± 1.0	13.0 ± 1.1*
Fetal hemoglobin (%)	12.4 ± 5.8	
HS-CRP (mg/L)	3.0 ± 2.6	1.1 ± 1.5*
MCH (pg)	30.1 ± 3.4	27.2 ± 2.1*
MCHC (g/dL)	32.4 ± 1.0	32.7 ± 1.1
MCV (fL)	92.7 ± 9.2	83.0 ± 5.5*
RDW (%)	20.0 ± 2.5	13.3 ± 1.1*
Total 25(OH)D (ng/mL)	19.2 ± 7.2	22.3 ± 9.3
On hydroxyurea (n [%])	9 (43)	

Mean ± SD (all such values).

BMI indicates body mass index; HS-CRP, high-sensitivity C-reactive protein; LBM, lean body mass; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; RDW, red blood cell distribution width; SCD-SS, type SS sickle cell disease; UAMA, upper arm muscle area; 25(OH)D, 25 hydroxyvitamin D.

*$P < 0.05$, SCD-SS versus Controls.

mass-for-height *Z* score (0.5 ± 0.6 vs. 0.01 ± 0.6), there were significant differences (all $P < 0.05$) in the following body composition variables: height *Z* score (0.1 ± 0.9 vs. −0.9 ± 1.1), weight *Z* score (0.2 ± 0.8 vs. −1.2 ± 1.1), BMI *Z* score (0.04 ± 1.1 vs. −1.0 ± 0.9), arm circumference *Z* score (−0.1 ± 1.1 vs. −1.5 ± 0.9), and UAMA *Z* score (0.2 ± 0.4 vs. −1.2 ± 0.9).

Unadjusted dominant hand maximum handgrip strength ($P < 0.01$) and peak power ($P < 0.04$) were significantly reduced in children with SCD-SS compared with healthy controls (Fig. 1). Using multiple regression analysis, a performance decrement persisted in dominant hand maximal handgrip strength (−4 kg) after adjusting for LBM and fat mass that together explained 66% of the variance (Table 2; LBM alone explained 65% of the variance). A deficit of 189.9 W persisted for peak power adjusted for age, LBM, fat mass and height explaining 91% of the variance (Table 3; LBM alone explained 89% of the variance).

Unadjusted MVC torques were significantly lower in children with SCD-SS compared with healthy subjects at 2 angles (both $P < 0.05$, Fig. 1). The deficit for subjects with SCD-SS persisted (−7.3 Nm) when the highest MVC torques (at 10-degree angle) were adjusted for left leg length, lean mass-for-height and fat mass-for-height *Z* scores using multiple regression, together explaining 65% of the variance (Table 4; left leg length alone explained 58% of the variance).

Hematologic and inflammatory status did not contribute significantly to the multiple regression models predicting any measure of muscle performance, and there were no differences found in performance by hydroxyurea use group (results not shown).

DISCUSSION

African-American children with SCD-SS compared with healthy African-American children of similar age and pubertal status had performance decrements in dominant hand maximum handgrip strength, peak power and plantar flexion isometric MVC torques. When measures were adjusted for body size and composition deficits, group differences were still evident. This underscores the importance of improving growth, body composition, and nutritional status in children with SCD-SS and suggests additional factors intrinsic and/or extrinsic to muscle tissue contributed to the reduced anaerobic performance. A previous study reporting that feeding a high-protein diet to transgenic sickle mice improved body composition and grip strength[16] provides direction for future studies.

Strength and power deficits have been shown in children with SCD-SS.[1,17] Findings from the present study agree with and extend previous work to show in a contemporary group of children with SCD-SS with almost half (9/21; 43%) taking hydroxyurea, body habitus–adjusted strength and power deficits were still present. Perna et al[18] using data from the 2011 to 2012 National Health and Nutrition Examination Study (NHANES) published nationally representative combined handgrip strength means and percentile distribution in US children by sex and age group. The maximal value from 3 trials per hand was summed to yield combined handgrip strength in pounds. We calculated combined handgrip strength in pounds from the present study for children with and without SCD-SS and compared with the means and percentile distribution by sex and age group from Perna et al.[18] Results, presented in Table 5 show that the children with SCD-SS consistently have a higher percentage in the lower percentile of the distribution of handgrip strength than healthy children. This is particularly evident in boys with 2/3 below the NHANES 20th percentile and 3/4 below the 50th percentile. Boys with SCD have previously been shown to have particularly large deficits in LBM, and these deficits increase through adolescence.[19] This supports findings from the present study suggesting strength deficits in children with SCD-SS. No study to date has assessed muscle torque in this population. We found reduced muscle torque, regardless of adjustment for commonly shown deficits in body size and composition in this group. Taken together, these performance deficits may result from factors intrinsic and/or extrinsic to the muscle, or by other yet to be elucidated factors.

Of the few exercise studies comparing children with SCD-SS to healthy children, the majority focused on aerobic performance. During an exhaustive cycle ergometer graded exercise test, work capacity, ejection fraction, and maximal cardiac output, heart rate, and blood pressure were lower in children with SCD-SS compared with healthy children.[20,21] To compensate for decreased oxygen-carrying capacity, children with SCD-SS extracted more oxygen resulting in a greater venous desaturation[22] and displayed an exaggerated ventilatory response partially due to increased physiological dead space during steady-state cycle ergometer exercise at 50% of their maximal workload.[23] Collectively these studies suggest a deficient cardiopulmonary response to aerobic exercise in children with SCD-SS compared with healthy children. These findings have significance as regular, moderate aerobic exercise is considered a good predictor of

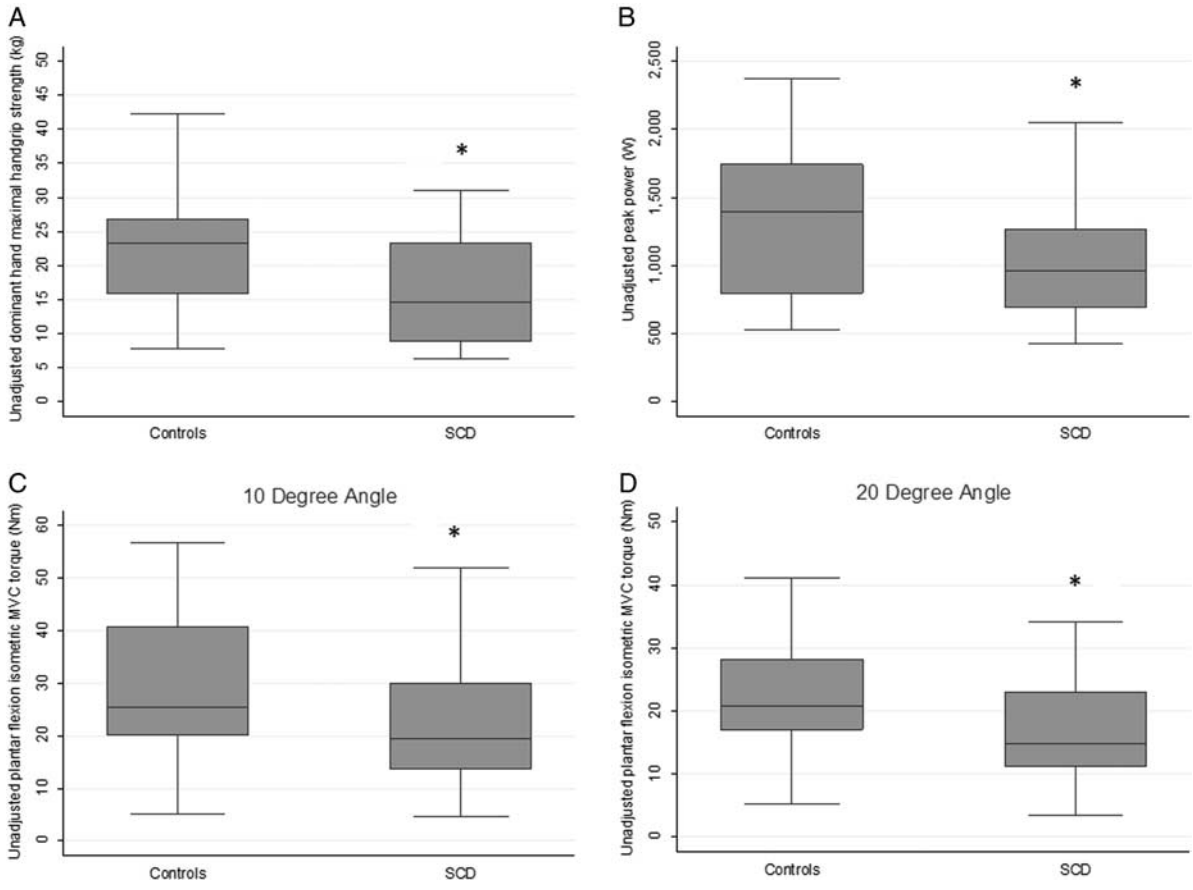

FIGURE 1. Boxplots showing that unadjusted values for dominant hand maximum handgrip strength (A), peak power (B), and plantar flexion isometric maximal voluntary contraction (MVC) torques at angles 10 degrees (C) and 20 degrees (D) were significantly reduced in children with SCD-SS compared with healthy controls (all $P > 0.05$). The top, bottom, and line through the middle of the box correspond to the 75th percentile (top quartile), 25th percentile (bottom quartile), and 50th percentile (median), respectively. The whiskers on the bottom extend from the 10th percentile (bottom decile) and top 90th percentile (top decile). MVC indicates maximal voluntary contraction; SCD, sickle cell disease. *$P < 0.05$, SCD versus Controls.

positive health outcomes in the general population. However, children's physical activity patterns are characterized by short bouts of high-intensity motion, requiring instantaneous energy release from intramuscular high-energy phosphates. As children engage in short-burst exertion when encouraged to be physically active, this form of movement should be part of assessments and targets to increase physical activity and quality of life in children. Anaerobic activity promotes muscle and bone development and thus is important for normal child development and lifelong health. However, there is a paucity of empirically based information comparing anaerobic exercise performance between children with SCD-SS and healthy children. In this study, the 3 measures used to evaluate anaerobic performance were all lower in children with SCD-SS versus healthy African-American children. Factors possibly contributing to these deficits will be outlined below.

Using a mouse model stimulation protocol, muscle mass independent maximal tetanic force and peak force

TABLE 2. Multiple Regression Model Predicting Dominant Hand Maximum Handgrip Strength

	Coefficient (kg)	SE	*t*	*P*	R^2
All (n = 44)					0.66*
SCD group	−4.0	1.8	−2.2	0.032	
LBM (kg)	0.7	0.1	6.7	0.001	
FM (kg)	−0.2	0.2	−1.4	0.160	
Constant	8.4	3.8	2.2	0.033	

*Lean body mass explained 65% of the variance.
FM indicates fat mass; LBM, lean body mass; SCD, sickle cell disease.

TABLE 3. Multiple Regression Model Predicting Peak Power

	Coefficient (W)	SE	*t*	*P*	R^2
All (n = 44)					0.91*
SCD group	−189.9	75.6	−2.5	0.017	
Age (y)	74.2	23.5	3.2	0.003	
LBM (kg)	73.7	9.5	7.8	0.001	
FM (kg)	−6.5	6.5	−1.0	0.325	
Height (cm)	−22.9	6.6	−3.5	0.001	
Constant	2058.5	598.5	3.4	0.001	

*Lean body mass explained 89% of the variance.
FM indicates fat mass; LBM, lean body mass; SCD, sickle cell disease.

TABLE 4. Multiple Regression Model Predicting Highest (at 10-Degree Angle) MVC Torque

	Coefficient (Nm)	SE	*t*	*P*	R^2
All (n = 44)					0.65*
SCD group	−7.3	3.3	−2.2	0.033	
LL length (cm)	1.8	0.3	5.5	0.001	
FM-for-height *Z* score	2.8	2.7	1.0	0.303	
LBM-for-height *Z* score	1.6	1.8	0.9	0.368	
Constant	−22.7	14.0	−1.6	0.112	

*Left leg length explained 58% of the variance.

FM indicates fat mass; LBM, lean body mass; LL length, left leg length; MVC, maximal voluntary contraction; SCD, sickle cell disease.

were reduced in SCD-SS versus control mice.[24] It was suggested that SCD associated oxidative stress reduces myofibrillar calcium sensitivity resulting in impaired calcium uptake by the sarcoplasmic reticulum, leading to impaired muscle function. The same authors showed increase intramuscular acidosis and a depletion of phosphocreatine concentration in addition to higher glycolytic enzyme activity during exercise in SCD-SS versus control mice.[25] It was speculated that the increased glycolytic contribution to adenosine triphosphate production was associated with hydrogen ion accumulation which has been shown to disrupt muscle function.[26] In addition, the faster depletion of phosphocreatine stores suggests perturbations in oxygen supply. These likely result from the commonly known SCD complications of chronic hemolytic anemia and arterial desaturation, or from low capillary density and tortuosity[27] or lower microvascular muscle oxygenation[28] in SCD. Deep tissue hyperalgesia has been proposed as an additional hypothesis contributing to muscle dysfunction given that analgesia improved muscle strength in SCD mice.[29] Through muscle biopsy of the vastus lateralis muscle, changes in fiber type distribution were observed in adults with SCD versus healthy adults (average age, 23 to 25 y) with a higher proportion of type I and a lower proportion of type IIa muscle fibers.[27] Some adults with SCD had intercellular adipocytes indicative of muscle degeneration suggestive of muscle wasting. Moreover, muscle atrophy, higher satellite cell number, and decreased activity of creatine kinase and several oxidative enzymes were found in adults with SCD versus controls. Any of these intramuscular factors alone or in combination could have contributed to the performance decrements observed in the present study. In addition, there are potential factors extrinsic to muscle that may also play a role and these will be outlined below.

TABLE 5. Comparison of Combined* Grip Strength (Pounds) From Present Study to Mean and Percentile Distribution by Sex and Age Group From 2011 to 2012 NHANES (Perna et al)[18]

	< 20 (%)		< 50 (%)	
	SCD-SS	Controls	SCD-SS	Controls
Male individuals	67	29	78	57
Female individuals	42	30	67	50

Sample sizes are 9 and 12 in SCD-SS sample and 13 and 10 in control sample for male individuals and female individuals, respectively.

*Maximal value from each hand (3 trials each) was summed to yield combined grip strength (pound).

NHANES indicates National Health and Nutrition Examination Survey; SCD-SS, type SS sickle cell disease.

In both children and adults with SCD-SS, autonomic nervous system impairment has been shown characterized by parasympathetic withdrawal and sympathetic predominance.[30–32] Although exercise is associated with autonomic nervous system activation by parasympathetic withdrawal and increased sympathetic activity, few studies have assessed if the sympathovagal imbalance present in SCD-SS might affect aerobic and/or anaerobic exercise performance. Alvarado et al[33] assessed autonomic system dysfunction by heart rate recovery after a maximal exercise test in subjects with SCD-SS ages 8 to 21 years. Results showed reduced heart rate recovery postexercise suggesting parasympathetic dysfunction and that the impairment becomes worse with age. In adults with SCD-SS, Martins et al[34] found no difference in the blood pressure or heart rate response to a maximal dominant handgrip strength test, whereby the subject maintained 40% of maximal strength for 90 seconds. However, these authors also showed that in response to 3 conditions (the valsalva maneuver, diving maneuver, and tilt test), cardiovascular autonomic dysfunction was present characterized by reduced baroreflex sensitivity and limited heart rate regulation via the parasympathetic nervous system.

Subclinical peripheral nerve involvement is an area of recent focus in SCD. In 1 study, the frequency of peripheral neuropathy was assessed in 51 children and adults with SCD-SS aged 15 to 51 years who had no clinically evident neurological signs and symptoms.[35] Peripheral nervous system involvement was observed in 20% of subjects including nerve conduction abnormalities, demyelination, and axonal degeneration. However, at the time of the nerve conduction assessments, 35 subjects were on hydroxyurea, 6 were on transfusion therapy, and 10 were not on specific SCD treatment. Electrophysiological studies of peripheral nerves are not routinely conducted in patients without clinical symptoms and thus the overall prevalence of subclinical peripheral nerve involvement in SCD is not well understood. Another possible factor could be that those with SCD-SS have a lower percentage of voluntary activation which could explain, at least in part, the lower muscle force production[36] and future studies should investigate this hypothesis.

In the clinical setting, empirical assessment of muscle performance, utilizing standardized protocols for reproducibility, is important for evaluation and treatment. Objective measures of muscle strength, power, and torque enable the clinician to determine the patient's current functional status while also forming the basis upon which a program for rehabilitation can be prescribed. The novel finding in the present study of a reduction in MVC torques in children with SCD-SS versus healthy controls provides a better understand of deficits in anaerobic ability beyond what is learned from handgrip strength and peak power that can help to guide clinical care interventions in this population. Torque is defined as force applied over a distance (lever arm) causing rotation about a fulcrum (axis of rotation). Simply stated, torque is what creates and drives biomechanical movement. Muscle torque is important in clinical care because the ability to maximize the amount of torque a muscle can generate enables optimal strengthening of the muscle. If the goal of treatment is to facilitate movement, the torque variables can be manipulated to

enhance muscle efficiency to move a body part. For example, previous exercise intervention studies have demonstrated improvements in the torque-angle relationship at the shoulder joint in young healthy subjects[37] and male soccer players.[38] Another study showing deficits in muscle torque in the 60 years and older group suggested including weight training or strength-endurance training to improve overall daily functioning.[39] Future research should investigate the efficacy of these and other exercise interventions to reverse MVC torque deficits in SCD-SS and should include patient-reported outcomes representation of these domains of physical function and quality of life.

Previously in children with SCD-SS peak power Z scores positively correlated with fetal hemoglobin (disease severity).[1] In the present study, hematologic or inflammatory status did not influence performance. A previous study conducted in SCD mice suggested that inflammatory status (at the muscle level) was not related to muscle dysfunction.[24] It is unclear if sample size, age, sex, or other factor(s) contributed to these differences in findings from the previous study and more research is need. We found no differences in performance when comparing those treated versus not treated with hydroxyurea therapy in the SCD-SS group, on hydroxyurea therapy in the SCD-SS group versus controls, or when all 3 groups were compared (SCD-SS on hydroxyurea, SCD-SS not on hydroxyurea and controls). Interestingly, for those treated versus not treated with hydroxyurea therapy in the SCD-SS group, although there were no significant differences in age, LBM-for-height Z score, or fat mass relative to height Z score, there were significant differences in height Z score, weight Z score, BMI Z score, arm circumference Z score, and UAMA Z score. It is unclear if the lack of an effect of hydroxyurea on performance could be attributed to sample size limitations, possible lack of changes in lean body or fat mass due to such a short study duration, variability in adherence to hydroxyurea, age, sex, or other factors and more research is warranted.

A limitation of the present study is that level of physical activity related to frequency, intensity or duration was not assessed. It has been previously suggested that the low physical activity level of patients with SCD could play a role in muscle repercussions related to remodeling of the microvascular, structural, and energetic characteristics of skeletal muscle.[27] Future research to assess the impact of low physical activity level on muscle perturbations in SCD is indicated.

In conclusion, after adjusting for growth and body composition deficits, maximal muscle strength, peak power, and MVC torques were reduced in children with SCD-SS compared with healthy control children. This suggests that additional factors contribute to attenuation in anaerobic performance.

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