

# Cardiopulmonary Fitness, Disease Severity, and Quality of Life in Children and Young Adults with Sickle Cell Anemia

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**BACKGROUND:** Poor physical functioning, low cardiopulmonary fitness, and low levels of physical activity are common among children and adults with Sickle Cell Anemia (SCA). Low fitness is an important predictor of morbidity and all-cause mortality in the general population. However, the relationship among cardiopulmonary fitness, physical activity, disease severity and quality of life in SCA has not been clearly established.

**OBJECTIVES:** To determine the clinical factors associated with low cardiopulmonary fitness in children and young adults with SCA. Our specific aims were: 1) to determine the relationship between cardiopulmonary fitness and health-related quality of life (HRQOL) measures of physical functioning (fatigue, mobility, daily physical activity) and 2) to determine the relationship among cardiopulmonary fitness, disease severity, and hydroxyurea (HU) use.

**METHODS:** Subject inclusion criteria included: 1) age 10-21 years old and 2) diagnosis of HbSS or S/ $\beta$ 0 thalassemia. Exclusion criteria included: 1) inability to perform CPET due to physical limitation; 2) enrollment on chronic transfusion program; 3) history of exercise-induced arrhythmia or syncope; 4) diagnosis of asthma 5) known exercise-induced bronchoconstriction (EIB). Matched controls were recruited among friends, relatives, and siblings to minimize socio-demographic variables that may impact baseline fitness. Primary outcomes included peak VO<sub>2</sub> (reference standard for fitness) measured by maximal cardiopulmonary exercise testing; fatigue and mobility assessment using NIH PROMIS® questionnaires; and self-reported physical activity using an adapted NHANES Physical Activity Questionnaire. Additional clinical data including vaso-occlusive pain episodes and acute chest syndrome events were obtained by electronic medical record review. Standard descriptive statistics and bivariate analyses were performed to examine the relationship of fitness to continuous and categorical variables.

**RESULTS:** In this preliminary analysis, 21 subjects (mean age 13.98 years) and 15 controls (mean age 16.53 years) across 2 institutions have been enrolled to date. Mean peak VO<sub>2</sub> levels were significantly lower in subjects compared to controls (24.10±5.64 vs. 28.97±8.59 mL/min/kg,  $p=0.048$ ). Peak VO<sub>2</sub> levels were significantly higher in subjects not on HU (28.32±4.33 vs. 22.41±5.30 mL/min/kg,  $p=0.035$ ). Mean parent-reported T-scores were significantly higher for subjects compared to controls on the PROMIS Fatigue Subscale (50.61±13.93 vs. 38.07±6.09,  $p=0.014$ ); mean T-scores for the pediatric (49.64±9.13 vs. 42.78±9.91,  $p=0.083$ ) and adult (45.05±8.84 vs. 38.08±5.66,  $p=0.167$ ) self-reported fatigue subscales were higher for subjects compared to controls, but did not reach significance. For the PROMIS Mobility Subscale, mean T-scores were significantly higher for subjects vs. controls across parent- (18.83±4.21 vs. 15.10±0,  $p=0.007$ ), pediatric- (19.45±4.04 vs. 15.50±0.95,  $p=0.009$ , and adult patient- (25.70±0.57 vs. 18.20±0,  $p=0.016$ ) reported subscales. For the NHANES questionnaire, a significantly higher proportion of subjects reported participating in at least 60 minutes of moderate-intensity physical activity per day compared to controls (38.1% vs. 20.0%,  $p=0.028$ ). Among subjects, there was no significant relationship between peak VO<sub>2</sub> and any functional capacity measures. Among controls, higher peak VO<sub>2</sub> significantly correlated with more number of days spent in vigorous-intensity physical activity (Spearman's rho=0.521,  $p=0.046$ ) and spent being physically active for at least 60 minutes (Spearman's rho=0.849 ( $p<0.001$ )). Among subjects, higher number of days spent in vigorous-intensity physical activity significantly correlated with lower self-reported levels of fatigue (Spearman's rho=-0.517,  $p=0.023$ ). There was no relationship between peak VO<sub>2</sub> and rates of clinical complications.

**CONCLUSIONS:** Enrollment is currently ongoing for this study. Preliminary findings demonstrate that children and young adults with SCA have lower cardiopulmonary fitness levels and overall, report significantly worse physical functioning compared to controls. A significantly higher proportion of patients with SCA met daily recommendations for moderate-intensity, but not vigorous-intensity, physical activity compared to controls. While there were no significant relationships between cardiopulmonary fitness and most measures of physical functioning or disease severity among patients with SCA, more days spent in vigorous-intensity activity was associated with lower levels of self-reported fatigue, which suggests that vigorous activity levels could be a useful measure of physical functioning in patients with SCA. Further analysis at the completion of this study is warranted to determine the utility of developing evidence-based exercise guidelines to improve cardiopulmonary fitness and to understand the impact of improved fitness on physical functioning and clinical disease severity in children and young adults with SCA.