**Abstract**

Background: Exercise intolerance is a common side-effect of treatment for childhood leukemia and lymphoma and contributes to adverse health and well-being during survivorship. While central, cardiovascular contributors to fitness have been shown to be impaired, the peripheral muscular factors have not been studied in this population. Therefore, peripheral muscular function in children after leukemia and lymphoma treatment remains unstudied.

Procedure: Eleven leukemia and lymphoma patients aged 8-18 years old who completed treatment 6-36 months prior and 11 healthy controls were included in analysis. $^{31}$P-MRS was used to characterize muscle bioenergetic metabolism at rest and after in-magnet knee extension exercise. General exercise capacity was assessed using a submaximal graded treadmill test and overall physical activity participation was assessed using the Habitual Activity Estimation Scale (HAES).

Results: The patients treated for leukemia and lymphoma exhibited lower anaerobic function (d=0.72), slower metabolic recovery (d=0.93), and lower mechanical muscle power (d=1.09) during in-magnet knee extension exercise compared with the healthy control group. Lower estimated $VO_{2peak}$ (41.61 ± 5.97 vs. 47.71 ± 9.99 $ml \cdot min^{-1} \cdot kg^{-1}$, d=0.76), lower self-reported minutes of physical activity (58.3 ± 35.3 vs. 114.8 ± 79.3 minutes, d=0.99) and higher minutes of inactivity (107.3 ± 74.0 vs. 43.5 ± 48.3 minutes, d=1.04, $p<0.05$) were also observed in the patient group.

Conclusion: Children treated for leukemia and lymphoma exhibit altered peripheral skeletal muscle energy metabolism in addition to previously reported central cardiovascular limitations during exercise. It is likely that both deconditioning and direct effects of chemotherapy treatment contribute to exercise intolerance in this population.

## Introduction

A common long-term effect of childhood cancer treatment is exercise intolerance [1] caused by disturbances to biochemical pathways necessary for skeletal muscle contraction [2], resulting in impaired aerobic fitness [3–6], lowered muscle strength and power [6–9] and/or poor motor coordination and balance [3, 7, 10].

The etiology of exercise intolerance is multifactorial in childhood cancer patients and survivors. Anthracycline chemotherapy agents have known cardiotoxic side-effects, which can impair stroke volume and central oxygen delivery [5, 6, 11, 12]. Peripherally at the skeletal muscle, many chemotherapy agents produce reactive oxygen species, which may damage microvasculature and mitochondria [1, 13], subsequently impairing peripheral oxygen delivery and aerobic respiration. Further, corticosteroids can cause muscle atrophy, reducing muscle mass, strength and other functionality [3, 12, 14, 15]. These direct disruptions to systems and tissues required to support muscle contraction and physical activity are compounded by indirect effects of treatment, as extended bed rest and fatigue can further exacerbate deconditioning and reduced physical function.

Physical activity habits and fitness level are independently associated with better physical health, including cardiovascular [16, 17], metabolic [17], and immunological function [17, 18], as well as lower risk of subsequent cancer [19–21]. Furthermore, improved fitness and physical activity contribute to better mental health, including lower risk and symptom severity of anxiety [22–25] and depression [23–28], improved mood [23, 27–29], vigour and overall higher quality of life [11, 30–32] in general population and pediatric cancer populations.

While central contributors to fitness, specifically cardiovascular function, have been shown to be impaired in childhood cancer patients [4, 5, 12], peripheral factors, such as skeletal muscle aerobic and anaerobic metabolism, have not been fully elucidated. The Fick Equation ($VO_2$ = Cardiac Output x arteriovenous $O_2$ difference) states that aerobic fitness ($VO_2$) is comprised of oxygen delivery - mediated by central cardiovascular function (Cardiac Output, CO = Heart Rate, HR x Stroke Volume, SV) - and oxygen extraction and use - mediated by peripheral muscular factors including activity of bioenergetic pathways (arteriovenous $O_2$ difference) [33]. While central cardiovascular impairment has been investigated in childhood cancer patients, peripheral pathophysiology of exercise intolerance in children after leukemia and lymphoma treatment requires further investigation.

Understanding central and peripheral contributors to overall exercise capacity is critical for evidence-based physical activity recommendations to be developed [34]. Recently, $^{31}$Phosphorus magnetic resonance spectroscopy ($^{31}$P-MRS) has been used to assess muscle metabolism in various populations with pediatric chronic diseases, including determining the function of creatine kinase, oxidative phosphorylation, and anaerobic glycolysis pathways during exercise and recovery [35–39]. Assessment of the high energy phosphorus containing metabolites within tissues using $^{31}$P-MRS, in conjunction with specifically designed exercise protocols, provides insight into bioenergetic and mechanical function of skeletal muscle, and furthers our understanding of exercise intolerance in pediatric cancer populations.

The objective of this study was to identify and quantify muscle metabolic limitations in childhood cancer patients compared with healthy controls. We hypothesized that compared to healthy controls, children treated for leukemia and lymphoma would have impaired peripheral skeletal muscle function, lower systemic aerobic fitness and report lower physical activity levels.

## Methods

### Participants

We recruited 11 patients (5 boys, 6 girls) from the Outpatient Leukemia/Lymphoma Clinic at The Hospital for Sick Children, Toronto, Canada and 11 age- and sex-matched controls. The inclusion criteria were a diagnosis of leukemia or lymphoma, completion of treatment within the previous 6-36 months, current age 8-18 years, no contraindication for exercise or magnetic resonance imaging (MRI), and no exposure to radiation treatment. This study was approved by the institutional Research Ethics Board and all participants and/or parents provided informed consent.

### Parameters of assessment

Height (cm) was measured using a free-standing Harpenden stadiometer (Holtain Ltd, Crosswell, Crymych, UK). Weight (kg) was measured using a Scaletronix digital scale (Model 5002, Welch Allyn, USA). Body mass index (BMI) was calculated using a BMI percentile calculator for children (https://www.cdc.gov/healthyweight/bmi/calculator.html).

The experimental procedures were conducted in the following sequence: 1) in-magnet exercise with $^{31}$P-MRS of peripheral skeletal muscle; 2) submaximal treadmill aerobic fitness testing; and

3) self-report of physical activity. A 30-minute break was given between MRI and treadmill procedures for recovery and all testing was completed within a 2-hour time period.

Magnetic Resonance Imaging (MRI) and $^{31}$P-MRS Assessments

Peripheral skeletal muscle function was examined using $^{31}$P-MRS of the vastus lateralis as previously reported [35,37]. Skeletal muscle data was collected using a 3.0T imaging and spectroscopy system (Siemens Healthineers, Ehrlangen, Germany) and acquired with a commercially available dual tuned 3.0T $^{31}$P transmit/receive surface coil. A calibrated, non-magnetic, up-down ergometer (Lode BV Medical Technology, Groningen, NL) was used to perform in-magnet exercise and acquisition of MR data at rest and following exercise.

Participants lay supine with their left knee bent and foot strapped into the pedal of the up-down ergometer. Anatomic scans were conducted to locate the voxel of interest of the vastus lateralis. Ten resting spectra were acquired and averaged for baseline concentration of phosphorous compounds. Once resting scans had been completed, participants completed a 30s knee-extension exercise at 100% intensity against a resistance load scaled to their body weight and further adjusted to ensure that a minimum of 10 revolutions per minute (RPM) could be achieved. A 5-minute rest was provided to allow metabolites and phosphagen compounds to return to baseline. The 5x30s exercise was then conducted against a resistance equivalent to 85% of the resistance established in the 30s bout. This protocol required participants to complete 30s of knee extension exercise for 5 repetitions with 15s of rest between each 30s bout. Spectra were obtained immediately following exercise bouts in the 15 second break between each of the 5 bouts of 30 seconds. Area under the curve was calculated for each phosphorus peak (Pi, PCr,

ATP γ, α, β peaks) using jMRUI v5.0 and line fitting for PCr recovery over time was completed using LabView. Technical details for MRS pulse sequences and post-processing analyses are provided in supplemental material.

Submaximal Aerobic Exercise Assessments

Aerobic fitness was measured using a submaximal walking test on a treadmill [43, 44]. Participants were required to walk at a self-selected fast walking pace at 0% incline on the treadmill for 4 minutes followed by a further 4 minutes at an incline of 5%. HR was recorded in the 3rd and 4th minute of each stage to ensure that a steady state had been attained. HR from steady state in the 0% and 5% stages were used to predict $VO_{2peak}$ according to Equation 1. Once complete, a 2-minute cool down was performed at a slow walking pace.

**Equation 1**

$$VO_{2peak} = -1772.81 + 318.64 \times [\text{sex}] + 18.34 \times [\text{weight}] + 24.45 \times [\text{height}] - 8.74 \times [\text{4-min HR}] - 0.15 \times [\text{weight}] \times [\text{HR difference}] + 4.41 \times [\text{speed}] \times [\text{HR difference}]$$

Variables: sex is female (0), male (1); weight is in kg; height is in cm; speed is in miles per hour; and HR difference is the change in bpm between the HR record in the 4th minute of 0% and 5% incline.

Habitual Physical Activity Estimation

Assessment of habitual physical activity was performed using the Habitual Activity Estimation Scale (HAES) [40]. The HAES is a self-report method of assessing daily physical activity,

previously used in many populations with pediatric chronic disease [41]. The HAES can be used to characterize time spent engaging in *Inactive* (lying down), *Somewhat Inactive* (sitting down), *Somewhat Active* (up and moving), or *Active* (moderate to vigorous activity) activities. Data were provided for a typical weekday and a typical Saturday and the average of each activity level was taken. Self-report of *Average Sleep* minutes was also provided, for total overall minutes of a 24-hour day (1440 minutes).

Data Analysis

Between group comparisons were made using independent t-tests for all $^{31}$P-MRS variables, predicted $VO_2$ and HR achieved on the submaximal treadmill test, and self-reported minutes of activity and sleep time. Normality of data was visually tested via Q-Q plot. A linear Q-Q plot was indicative of normally distributed data. Homoscedacity was tested using Levene's test in which a significance of <0.05 was taken to be heteroscedastic. Effect sizes were calculated by Cohen's d using mean difference and pooled variance for all variables as the sample size was low. Calculating effect sizes is a quantitative method used to describe the magnitude of difference between two measures, as opposed to p-values, or other probabilistic statistics, which provide a statistical significance indicating how likely it is that a difference exists between the two measures. Using a standardized mean difference, a Cohen's d of 0.2 or less is considered to indicate no effect, 0.2-0.5 to indicate a small effect, 0.5-0.8 to indicate a medium effect, and 0.8-1.0 to indicate a large effect. All statistical analyses were performed using SPSS version 24 (IBM, USA).

**Results**

Participants

All participants completed each component of the study protocol. Participant characteristics for both groups are shown in Table 1. There were no statistical differences between groups for age, height, weight or BMI. Diagnosis and treatment characteristics for the patient group are presented in Table 2.

$^{31}$P-MRS resting measures results

$^{31}$P-MRS variables were assessed at rest, and the results were analyzed as the average of 8 resting spectra collected sequentially. No significant differences between groups on $^{31}$P-MRS variables were observed at rest ($p>0.05$, Table 3).

$^{31}$P-MRS results during 5x 30 seconds exercise

$^{31}$P-MRS data were collected immediately before exercise, after each of 5 x 30-second exercise bouts and during recovery (Table 4). Average RPM over the 5x30s exercise repetitions was significantly higher in the healthy control group (9.2 ± 3.1 vs. 6.0 ± 2.0 rpm, $p<0.05$; Table 4). No other statistically significant differences were observed between groups for $^{31}$P-MRS variables in response to 5x30s exercise bouts. However, there was a trend towards higher average power (6.4 ± 1.7 watts vs. 5.2 ± 0.5 watts, $p=0.09$) and higher average Pi/PCr ratio over 5x30s repetitions (2.61 ± 1.68 vs. 1.59 ± 0.52, $p=0.08$) in the healthy control vs. the patient group.

Effect sizes for peripheral aerobic fitness variables determined by Cohen's d indicated a small effect size (i.e., standardized mean difference between the two groups) for ATP production rate

by oxidative phosphorylation (d=0.20). Moderate effect sizes for average pH change post-exercise (d=0.59), ATP production rate by anaerobic glycolysis (d=0.72), and total ATP production rate (d=0.68) were determined. Large effect sizes were found for PCr recovery time-constant (d=0.80), average Pi:PCr ratio (d=0.93), average power achieved (d=1.09), average RPM achieved (d=1.23), and average power scaled to body mass (d=1.00). Results, group differences, and effects sizes are shown in Table 4.

Submaximal aerobic exercise test results

All participants completed the submaximal exercise test on the treadmill. No significant differences in $VO_{2peak}$ ($p>0.05$) or walking speed ($p>0.05$) were observed between groups. The patient group demonstrated higher HR at 5% incline (159.3 beats·min$^{-1}$ vs. 143.7 beats·min$^{-1}$) and higher HR change from rest to 5% incline (75.2 beats·min$^{-1}$ vs. 56.9 beats·min$^{-1}$), though this did not reach statistical significance ($p=0.15$). However, effect sizes for systemic aerobic fitness variables determined by Cohen's d indicated moderate effect sizes for HR at 5% incline (d=0.64) and estimated relative $VO_{2peak}$ (d=0.76). Results, group differences, and effects sizes are shown in Table 5.

Habitual physical activity estimation scale results

All participants completed the HAES questionnaire. Self-report of minutes spent Inactive, Somewhat Inactive, Somewhat Active, or Active were averaged between weekend and weekdays and reported in Table 6. Statistically significant group differences were found for Inactive Minutes, which was higher in the patient group (107.3 ± 74.0 minutes vs. 43.5 ± 48.3 minutes, $p<0.05$). No other significant differences were found between groups for physical activity or

sleep minutes ($p>0.05$; Table 6). However, a large effect size was determined by Cohen's d for Active Minutes ($d=0.99$), Inactive Minutes ($d=1.04$), and Sleep Minutes ($d=0.92$), while moderate effects sizes were found for Somewhat Inactive Minutes ($d=0.64$). Results, group differences, and effects sizes are shown in Table 6.

## Discussion

We used $^{31}$P-MRS as a non-invasive means of investigating the physiological pathways supporting skeletal muscle function during a knee-extension exercise in children following treatment for leukemia or lymphoma. This method measures relative concentration of phosphorus metabolites in a voxel of skeletal muscle to quantify energy production by CK, anaerobic glycolysis, and oxidative phosphorylation, as well as metabolic stress by change in energy charge of the cell and pH buffering [35–37]. The results of the current study indicate both lower aerobic and anaerobic metabolic function of the quadriceps muscle in the patient group vs. healthy controls. As well, the patient group demonstrated a lower ability to generate metabolic effort and mechanical power compared to healthy controls, indicated by smaller end-exercise Pi:PCr ratio and change in pH, and smaller wattage achieved during testing, respectively. In our previously published pilot study of pediatric hematopoietic bone marrow transplant recipients, we found similar impairment the patient group's power output during a 5x30s knee extension exercise (6.2 Watts vs. 9.4 Watts in the healthy control group), as well as lower metabolic effort indicated by lower end-exercise Pi:PCr ratio [36].

A comparison with studies that measured skeletal muscle function using $^{31}$P MRS in other pediatric clinical groups, including girls with Turner Syndrome [35], children with Cystic

Fibrosis (CF) and Primary Ciliary Dyskinesia (PCD) [37], and Idiopathic Juvenile Dermatomyocytis (JDM) [39], suggest that children treated with cancer have unique skeletal muscle bioenergetic pathology and greater disruption to contractile function of skeletal muscle. For example, girls with Turner Syndrome achieved similar workloads to healthy controls and no impairment in aerobic pathways, however greater metabolic exertion (Pi:PCr) and acidosis was observed as well as impaired anaerobic glycolytic function [35]. Similarly, children with CF had greater acidosis with exercise and slower aerobic ATP regeneration but were able to achieve similar workloads and metabolic efforts to healthy controls, while children with PCD demonstrated similar metabolic impairments in addition to lower mechanical output (workload achieved), even when scaled to muscle mass, which was attributed to pH related disruption to contractile function [37].

Our findings showed specific impairments to both the anaerobic pathways, similar to girls with Turner Syndrome, and aerobic pathways, similar to children with CF and PCD. However, our patient group also appeared to demonstrate lower workloads and lower metabolic exertion compared to these other pediatric clinical populations, indicating more significant peripheral disturbance to physiological processes underlying skeletal muscle contraction. This suggests a more global disruption to skeletal muscle function, impairing multiple metabolic pathways and overall ability to produce metabolic effort and subsequent contractile force and power output. Two possible etiologies of exercise intolerance may warrant further investigation: the use of glucocorticoids have known atrophic effects on skeletal muscle, with high force producing, anaerobic type II muscle fibers being most vulnerable [12, 14, 15]; and disuse atrophy associated with the intensive and prolonged treatments associated with leukemia and lymphoma may be

mechanistic in the peripheral dysfunction observed in our patient group relative to other pediatric clinical groups.

Importantly, in the current study the lower metabolic perturbation observed in our patient group was accompanied by slower PCr recovery (d=0.80), suggesting that the patient group was not only less able to generate metabolic effort during exercise but also exhibited less effective metabolic recovery following exercise. These findings may translate to functional deficits characterized by lower ability to engage in high intensity activities and longer rest periods required between high intensity bouts. This is particularly relevant as many childhood activities involve intermittent bouts of high intensities, such as stop and go sports and other childhood games [45].

In line with previous studies investigating systemic aerobic fitness in childhood cancer patients, we observed a moderate effect size (d=0.76) for estimated relative $VO_{2peak}$ between the patient group and the healthy controls. However, compared to prior studies, our patients presented with a higher $VO_{2peak}$ that places them in a healthier aerobic fitness range. More specifically, previous studies have observed $VO_{2peak}$ in childhood cancer patients to be in the range of 35.1 $ml \cdot min^{-1} \cdot kg^{-1}$ to 42.5 $ml \cdot min^{-1} \cdot kg^{-1}$ [4, 5, 12] compared with our findings of 41.6 $ml \cdot min^{-1} \cdot kg^{-1}$ in the patient group and 47.7 $ml \cdot min^{-1} \cdot kg^{-1}$ in the healthy control group. The submaximal test we used in the current study to estimate $VO_{2peak}$ may have resulted in slightly higher estimated values for $VO_{2peak}$. Despite higher estimated values in our study, we found the magnitude of decrement in the patient group to be in line with previous studies. On average, $VO_{2peak}$ was 6.1 $ml \cdot min^{-1} \cdot kg^{-1}$ (14.7%) lower in the patient group than the healthy control group, which is similar to the

magnitude of difference observed in a meta-analysis of aerobic fitness in pediatric cancer patients of 5.97 $ml \cdot min^{-1} \cdot kg^{-1}$ (13%) [12]. Interestingly, self-selected walking speed was the same between groups, although mean HR required to sustain walking speed at 5% incline was higher in the patient group, suggesting their chosen pace represented a higher relative workload. Previous studies of children treated for childhood cancer have found that exposure to anthracyclines causing cardiotoxicity contributes to central impairments to aerobic fitness [5], which may have been the case in our patient group, however, the homogeneity of the patient group with respect to treatments did not permit exploration of this possibility.

We found habitual physical activity to be lower in the patient group compared with healthy control group, as indicated by a large effect size of d=0.99. On average, the patient group reported 56.5 fewer Active Minutes per day and 63.8 greater Inactive Minutes per day compared with HC. This is meaningful given that the physical activity guidelines for children recommends 60 minutes per day of moderate to vigorous physical activity (MVPA). Previous studies of physical activity habits in childhood cancer patients compared to healthy siblings reported similar findings. Warner et al (1998) reported lower total daily energy expenditure in patients (159 $kJ \cdot day^{-1}$), which was attributed to lower physical activity habits, specifically in higher intensity, MVPA minutes [46]. Similarly, in a previous pilot study of children receiving hematopoietic bone marrow transplantation, the patient group demonstrated lower minutes of activity and higher minutes of inactivity in the patient group, although this was only the case in weekend days [36].

In summary, our hypotheses were confirmed as effect sizes determined by Cohen's d showed evidence of lower peripheral skeletal muscle function, as well lower systemic aerobic fitness and lower habitual physical activity levels in childhood leukemia and lymphoma patients post-treatment compared to an age and sex-matched healthy control group. However, it is important to note that T-tests revealed no statistical differences in group means. A post-hoc power calculation using PCr recovery time as the primary outcome variable and indicated low statistical power. Therefore, it is not surprising that despite large effect sizes indicated by the difference in standardizes means between the groups, probabilistic statistics did not reveal many statistically significant differences between groups. While the low statistical power for probabilistic hypothesis testing is undoubtedly a limitation of the present study, given the sophisticated nature of the study methodology and in depth requirements for participants, as well as similar sample sizes from other $^{31}$P MRS based studies in children [35–39, 47] we feel the findings of the study show clinically meaningful differences between children treated for leukemia and lymphoma, which have important implications for their physical health and function during survivorship.

There are several additional limitations to the current study. Our patient sample was homogeneous in regards to diagnosis and treatment such that no inferences could be made about the differential effect of chemotherapy agents on skeletal muscle function and exercise intolerance (i.e., glucocorticoid effect on peripheral type II muscle fibres vs. anthracycline effect on cardiovascular function). While our $VO_{2peak}$ findings were well in line with previous research, we used a submaximal test to ensure all participants would be able to complete testing, however, a maximal test may have provided greater accuracy. Similarly, we used a self-report of physical

activity habits, which could have been more accurately assessed by quantitative means, such as accelerometry or other activity tracking.

## Conclusions

Taken together, our findings confirm exercise intolerance as a side-effect of childhood leukemia and lymphoma and implicate peripheral skeletal muscle dysfunction as a contributor, in addition to other systemic and central factors. Children treated for leukemia and lymphoma experience a higher relative exertion at lower absolute intensities and are unable to produce higher outputs due to impairments to muscle strength and anaerobic function of skeletal muscle. These impairments in conjunction with slower metabolic recovery due to lower aerobic metabolic function of skeletal muscle, are likely to make higher intensity or variable intensity activity especially challenging for childhood cancer patients and survivors and may contribute to lower engagement in moderate to vigorous physical activity, which may further contribute to global physical deconditioning, thereby establishing a cycle of physical deconditioning that may have significant long-term health and functional implications. Addressing exercise intolerance in children following cancer treatment is important, and both peripheral physiological side-effects in addition to central mechanisms should be considered when developing rehabilitative strategies to support the recovery of physical fitness and a healthy lifestyle.

## Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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