Reduced Fat Oxidation Rates During Submaximal Exercise in Adolescents with Crohn's Disease

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Background: Children with Crohn's disease (CD) suffer from malnutrition. Understanding substrate utilization during exercise may help patients with CD sustain a healthy active lifestyle without compromising nutrition. The aim of this study was to determine whether substrate utilization and bioavailability during exercise are altered in children with CD compared with controls.

Methods: Seven children with CD (mean age ± SD: 15.2 ± 2.3 yr) and 7 controls (14.4 ± 2.3 yr) were matched by sex and biological age. Participants completed 60 minutes of cycling at an intensity equivalent to 50% of their peak mechanical power. Rates of total fat and carbohydrate (CHO) oxidation, the amount of fat and CHO oxidized, and the contribution of fat and CHO to total energy expenditure were calculated from expired gases collected during exercise. Blood was collected before, during, and at the end of exercise and analyzed for insulin, free fatty acids, and glucose.

Results: Whole-body fat oxidation rate (expressed in mg · kg^{-1} of body weight per min) during exercise was lower in children with CD (5.8 ± 1.0) compared with controls (8.0 ± 2.2, $P < 0.05$). Children with CD relied significantly more on CHO, with approximately 10% greater contribution toward total energy expenditure ($P < 0.05$) than controls. There were no differences in plasma insulin, free fatty acids, or glucose between the groups.

Conclusions: Fat metabolism during exercise seems to be impaired in children with CD. A greater reliance on CHO is required to meet the energy demands of submaximal exercise.

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Key Words: substrate utilization, fat oxidation, exercise, children, Crohn's disease

Children with Crohn's disease (CD), a chronic inflammatory disease,[1] tend to suffer from malnutrition leading to impaired growth.[2] Malnutrition in CD is thought to occur as a result of reduced caloric intake, as opposed to excessive energy requirements or expenditure,[3] with pediatric patients consuming only 54% of recommended total calories on a daily basis.[4] This energy deficit has been linked with reduced levels of IGF-1, a growth mediator, contributing to impaired growth.[5] Enteral nutrition[6] or altered diets[7] seem to have positive clinical outcomes with improvements in growth[6] and reductions in inflammation.[6,7] Promising findings such as these have led to the promotion of nutritional therapy in children with CD,[4,8] suggesting that these patients have unique nutritional requirements when compared with the general population.

Although there is no literature on the benefit or harm of exercise in children with CD, its therapeutic effects are evident in adult patients with reports of improvements in quality of life, stress, and disease activity based on the Inflammatory Bowel Disease Quality of life index, the Inflammatory Bowel Disease Stress Index, and the Harvey–Bradshaw Simple Index of Crohn's Disease activity, respectively.[9,10] Furthermore, exercise in patients with CD is also proposed to induce anti-inflammatory effects, counteract bone mineral losses, and reduce pain, fatigue, and intestinal problems.[11] If, in fact, these benefits translate to children with CD, exercise may serve as a potent form of therapy in this population. It is important to note, however, that because children with CD suffer from a poor nutritional statue, promoting regular exercise as a therapy would only be of value if it does not further compromise adequate nutritional intake and consequently growth.

Substrate utilization during exercise has not yet been investigated in either adults or children with CD. However, under resting conditions, adults in remission demonstrated higher fat oxidation rates compared with healthy controls.[12] This altered metabolism may be associated with an inflammation-mediated inhibition of insulin secretion, which is known to play an important role in regulating glucose[13] and fat metabolism.[14,15] Thus, given the chronic inflammatory state of patients with CD,[16] examining metabolic hormones in this population may give insight into

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the regulation of substrate utilization at rest and during exercise. The downstream effects of insulin can be further assessed by the bioavailability of different energy substrates, including plasma free fatty acids (FFA) and glucose, during exercise.

The goal of this study was to provide an initial assessment of substrate utilization during exercise in youth with CD. A better understanding of substrate utilization during exercise may provide clinicians and patients with valuable information to guide appropriate diet habits to support an active lifestyle while maintaining healthy growth and development. Therefore, the specific objectives of this study were (1) to determine whether substrate utilization, in particular the use of fat and carbohydrates (CHO) as fuel, during submaximal exercise is altered in youth with CD compared with a group of healthy controls, and (2) to examine the effect of exercise on plasma insulin, FFA, and glucose in these 2 groups.

METHODS

Participants

Seven children with CD in remission and 7 healthy controls participated in this study. Children with CD were recruited from the Centre for Child and Youth Digestive Health at the McMaster Children's Hospital in Hamilton, Ontario, Canada. Patients included in this study were those who were in remission as determined by a score <10 on the Pediatric Crohn's Disease Activity Index. Exclusion criteria were active disease as determined by Pediatric Crohn's Disease Activity Index within the previous 2 weeks, and in females, the use of any form of contraceptives. Healthy biological age- and sex-matched controls were recruited from the community. Given that substrate utilization during exercise is influenced by biological maturity,[17] and previous reports of later onset maturity in youth with CD,[18] we elected to match our participants by biological age rather than chronological age. However, Tanner staging of pubic hair development was self-assessed for descriptive purposes only. Biological age was defined as the estimated years to age of peak height velocity.[19] This study was approved by the Hamilton Health Science/Faculty of Health Science Research Ethics Board. Parents/guardian and youths singed a consent and assent form, respectively, before induction into the study.

Experimental Design

Details of this study's experimental design have been published previously.[16] Briefly, participants completed 2 visits. During visit 1, anthropometric variables (height, weight, and body composition) were measured along with peak oxygen uptake ($\dot{V}O_{2peak}$) and peak mechanical power, assessed using the McMaster All-Out Progressive Continuous Cycling Test, as previously described.[16] Visit 2 was scheduled a minimum of 2 to 3 days after visit 1, with testing occurring after school (4 to 6 PM) on weekdays or in the afternoon on weekends. Participants were asked to refrain from consuming any food or liquid, with the exception of water, 3 hours before the visit. They also avoided "fast food" and refrained from strenuous physical activity for at least 24 hours before the visit. Visit 2 consisted of 2 × 30-minute bouts of cycling at a constant pace of 60 rpm and an intensity equivalent to 50% peak mechanical power. Participants were given a 6-minute rest period between the bouts. Breath-by-breath gas exchange ($\dot{V}O_2$ and $\dot{V}CO_2$) was assessed (Vmax29; SensorMedics, Palm Springs, CA) over a 6-minute period from 12 to 18 minutes (EX1 bout 1; EX3 bout 2) and 23 to 29 minutes (EX2 bout 1; EX4 bout 2) of each 30-minute bout. The last 3 minutes of each gas collection period were averaged and used for analysis. Blood samples were collected through an indwelling catheter placed in the median cubital vein. Sampling time points included before exercise (REST), the midpoint of exercise during the 6-minute rest period (MID), and the end of exercise (END). All plasma samples were aliquoted and stored at −80°C until analysis.

Substrate Calculations

Whole-body oxidation rates of total fat and total CHO were calculated using the following equations[20]:

$$FAT_{total}\,(g/min) = 1.70\ \dot{V}CO_2\,(l/min) + 1.69\ \dot{V}O_2\ (l/min)$$

$$CHO_{total}\,(g/min) = 4.59\ \dot{V}CO_2\,(l/min) + 3.23\ \dot{V}O_2\ (l/min).$$

The energy potentials of fat (9.75 kcal/g) and CHO (3.87 kcal/g) were used and expressed as a percent of total energy expenditure (EE). In addition, the amounts of fat and CHO oxidized, expressed in grams, were determined using area under the curve (Prism; GraphPad, La Jolla, CA) and were based on rates of oxidation at EX1, EX2, EX3, and EX4.

Blood Analyses

Plasma insulin and FFA were analyzed using enzyme-linked immunochemistry substrate assay kits (Life Technologies, Inc., Burlington, ON, Canada, and Zen-Bio, Inc., Research Triangle Park, NC, respectively). Plasma glucose was analyzed using colorimetric assay kits (Cayman Chemical Company, Ann Arbor, MI). All exercise concentrations were corrected for changes in plasma volume.[21]

Statistical Analysis

Data were tested for normality using a Shapiro–Wilk test ($P < 0.05$, PASW Statistics 17; SPSS, Inc., Chicago, IL). Tanner stage, height, body mass index percentile, and CHO oxidized did not have normal distribution and were tested using Mann–Whitney U tests to compare groups. Age, estimated years from peak height velocity, all other anthropometric measures, percent of body fat, $\dot{V}O_{2peak}$, relative intensity, and fat oxidized were normally distributed and underwent independent t tests were used to compare groups. Rates of FAT_{total} and CHO_{total} oxidation, percent of fat to total EE, percent of CHO to total EE, and plasma glucose concentration were normally distributed. Plasma insulin and FFA data were log transformed to achieve normality, and log values were

used for all subsequent statistical analyses. One-way analysis of covariance (Statistica version 5.0) was used to examine the effect of exercise on FAT_{total} oxidation rate, CHO_{total} oxidation rate, %fat of total EE, %CHO of total EE, insulin, glucose, and FFA, with the participant's relative exercise intensity used as the covariate. Two-way repeated-measures analyses of covariance were performed to determine between group differences (CD versus control) in FAT_{total} oxidation rate, CHO_{total} oxidation rate, %fat of total EE, %CHO of total EE, insulin, glucose, and FFA throughout the session (i.e., EX1, EX2, EX3, and EX4, or REST, EX, and REC). Tukey's HSD post hoc analyses were performed where appropriate to examine specific mean differences. Significance was set at $P < 0.05$. Effect sizes were calculated using the equation effect size = (mean of group 1 − mean of group 2)/pooled SD. Calculations were completed for total rate of fat oxidation, fat oxidized, total rate of CHO oxidation, CHO oxidized, and energy contribution to fat and CHO. Unless otherwise stated, data are presented as mean ± SD.

RESULTS

Participants

Participant characteristics are presented in Table 1. All patients with CD scored 0 on the Pediatric Crohn's Disease Activity Index and had a mean disease duration of 2.0 ± 1.1 years. Three patients had terminal ileum Crohn's, 2 had ileal colonic Crohn's, 1 patient had ileo-Crohn's, and 1 had colonic Crohn's. Two patients had been or were currently on steroid therapy with a lifetime dosage of 3.99 and 2.24 g, respectively. None of the participants were on anti–TNF-α therapy. At baseline, children with CD had a significantly lower weight percentile and aerobic fitness ($\dot{V}O_{2peak}$) compared with controls. During the 2 × 30-minute bouts of cycling, $\dot{V}O_2$ expressed as a percent of $\dot{V}O_{2peak}$ was significantly higher in CD compared with controls. All other variables were similar between the groups.

TABLE 1. Participants Characteristics

	Controls (n = 7)	CD (n = 7)	*P*
Age	14.4 ± 2.3	15.2 ± 2.3	0.55
Estimated years from PHV	1.0 ± 2.2	1.1 ± 2.2	0.95
Tanner stage	3.7 ± 1.4	3.6 ± 1.3	0.81
Height	1.7 ± 0.2	1.7 ± 0.1	0.62
Height percentile	70.7 ± 30.7	44.9 ± 19.3	0.08
Weight	57.6 ± 16.5	53.0 ± 12.2	0.56
Weight percentile	60.6 ± 20.7	35.7 ± 21.2	**0.046**
BMI	19.5 ± 3.1	18.8 ± 2.0	0.63
BMI percentile	45.5 ± 24.9	31.2 ± 20.1	0.26
Body fat, %	13.7 ± 10.1*	15.0 ± 3.9	0.74
$\dot{V}O_{2peak}$ ($mL \cdot kg^{-1} \cdot min^{-1}$)	53.5 ± 4.6	43.1 ± 6.5	**0.01**
Relative intensity ($\dot{V}O_2$, %)	63.0 ± 4.5	71.0 ± 5.8	**0.01**

Values are expressed in mean ± SD. Tanner stage was completed using a self-assessment of pubic hair development. Height, weight, BMI percentile reference values were obtained from stature-for-age and weight-for-age data files from the Centre and Disease Control, respectively. Percent body fat was calculated using an age-specific bioelectrical impedance analysis equation.
Significant difference between the groups are indicated with bold text.
*n = 6.
PHV, peak height velocity; BMI, body mass index.

Oxidation Rates

Rates of FAT_{total} oxidation (expressed in $mg \cdot kg^{-1}$ of body weight per min) in CD increased from EX1 (3.2 ± 1.6) to EX2 (4.9 ± 1.1, $P < 0.01$), EX3 (7.3 ± 1.1, $P < 0.001$), and EX4 (7.6 ± 1.0, $P < 0.001$) (Fig. 1A). Similarly, rates of FAT_{total} oxidation increased in controls from EX1 (5.5 ± 1.8) to EX2 (8.1 ± 3.1, $P < 0.01$), EX3 (8.6 ± 2.5, $P < 0.001$), and EX4 (10.0 ± 2.1, $P < 0.001$) (Fig. 1A). Compared with controls, those with CD demonstrated a significantly lower rate of FAT_{total} oxidation (main effect for group, CD: 5.8 ± 1.0, controls: 8.0 ± 2.2, $P < 0.05$) (Fig. 1C). In addition, the total amount of fat oxidized (area under the curve) was reduced in those with CD compared with controls (17.6 ± 3.1 g versus 24.4 ± 7.0 g, $P < 0.05$) (Fig. 2A). Effect sizes between the 2 groups for the rate of FAT_{total} oxidation and fat oxidized was 1.08 for both variables.

Rates of CHO_{total} oxidation (expressed in $mg \cdot kg^{-1}$ of body weight per min) in CD were similar between EX1 (37.8 ± 8.5) and EX2 (35.2 ± 7.0), but decreased from EX1 to EX3 (29.9 ± 8.3, $P < 0.001$) and EX4 (28.3 ± 7.7, $P < 0.01$) (Fig. 1B). In controls, CHO_{total} oxidation decreased from EX1 (32.7 ± 4.6) to EX4 (23.6 ± 1.4, $P < 0.01$), whereas rates at EX2 (27.8 ± 6.6) and EX3 (28.7 ± 3.4) were similar to EX1 (Fig. 1B). Compared with controls, those with CD demonstrated a similar rate of CHO_{total} oxidation (32.8 ± 7.2 versus 28.2 ± 2.9) (Fig. 1D). Total amounts of CHO oxidized (area under the curve) were also similar between CD and controls (98.1 ± 21.9 g versus 84.7 ± 10.0 g) (Fig. 2B). Effect sizes between the 2 groups for the rate of CHO_{total} oxidation and fat oxidized were 0.78 and 0.76, respectively.

Energy Yield

The percent of EE from fat in children with CD increased significantly from 18% ± 8% at EX1 to 39% ± 10% at EX3 ($P < 0.001$) and 41% ± 8% at EX4 ($P < 0.001$), whereas the percent of EE from fat at EX2 (26% ± 7%) was not significantly different from EX1. The percent of EE from fat in controls increased from 30% ± 9% at EX1 to 42% ± 15% at EX2 ($P < 0.05$), 42% ± 9% at EX3 ($P < 0.01$), and 51% ± 5% at EX4 ($P < 0.001$). The percent of EE from CHO in children with CD decreased from 82% ± 8% at EX1 to 61% ± 10% at EX3 ($P < 0.001$) and 59% ± 8% at EX4 ($P < 0.001$), whereas EX2 (74% ± 7%) was similar to EX1. The percent of EE from CHO in controls decreased from 70% ± 9% at EX1 to 58% ± 15% at EX2 ($P < 0.05$), 58% ± 9% at EX3 ($P < 0.01$), and 49% ± 5% at EX4 ($P < 0.001$). Children with CD relied significantly less on fat and more on CHO compared with healthy children (fat: 31% ± 7% versus 41% ± 8%, $P < 0.05$; CHO: 69% ± 7% versus 59% ± 8%,

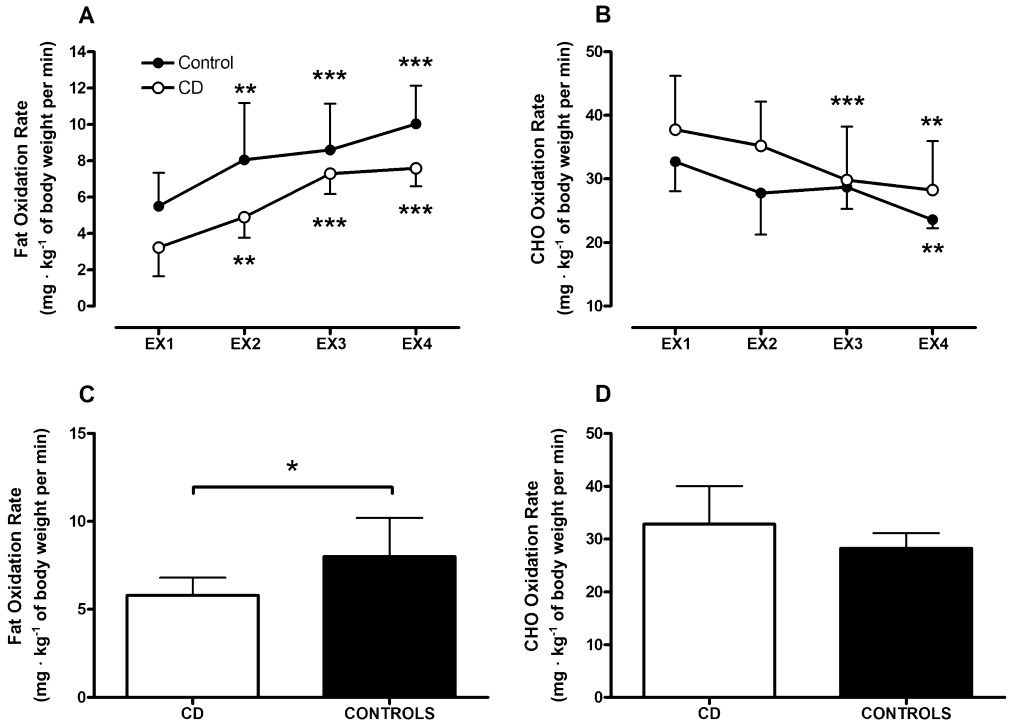

FIGURE 1. A, Fat oxidation rates in children with CD and controls. B, CHO oxidation rates in children with CD and controls. C, Average fat oxidation rates. D, Average CHO oxidation rates. Values are expressed in mean ± SD. Exercise consist of 2 × 30-minute bouts of cycling. EX1, midway of the first bout; EX2, at the end of the first bout; EX3, midway of the second bout; EX4, at the end of the second bout. *Significantly different between groups, $P < 0.05$. Significantly different from EX1, **$P < 0.01$; ***$P < 0.001$.

$P < 0.05$) (Fig. 3). Effect sizes between the 2 groups for the percent of EE from fat and from CHO was 1.10 for both variables.

Insulin

Insulin concentrations (reported as back-transformed means [95% confidence interval] in pmol/L) were similar between groups and were not affected by exercise in either CD (n = 6, REST: 130.2 [83.9–202.1], MID: 100.1 [77.5–129.3], END: 80.8 [63.9–102.2]) or controls (n = 6, REST: 97.5 [72.9–130.4], MID: 69.1 [45.3–105.3], END: 82.2 [56.2–120.1]).

Plasma FFAs

In children with CD, FFA concentrations (reported as back-transformed means [95% confidence interval] in μM) increased from REST (233.9 [112.2–487.3]) at MID (404.7 [245.5–666.9], $P < 0.05$) and END (667.7 [364.6–1222.9], $P < 0.001$). FFA concentration also increased in controls from REST (281.8 [140.60–565.1] μM) at MID (472.3 [258.8–858.6], $P < 0.05$) and END (948.2 [577.0–1558.2], $P > 0.001$). Plasma FFA concentration was similar between the groups at all time points.

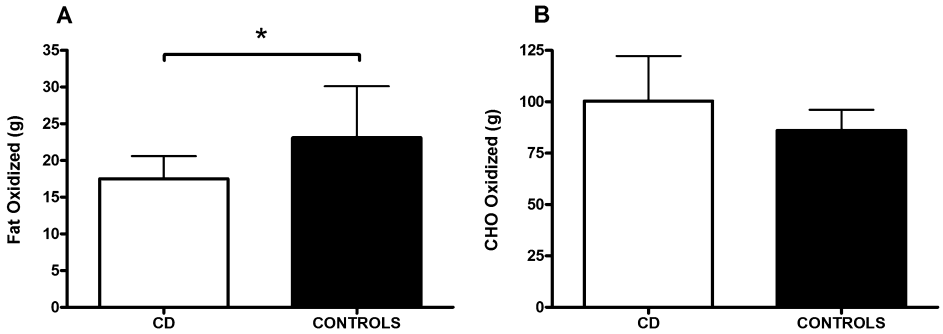

FIGURE 2. A, Amount of fat oxidized by children with CD and controls. B, Amount of CHOs oxidized by children with CD and controls. Amount of substrate oxidized was determined using area under the curve. Values are expressed in mean ± SD. *Significantly different between groups, $P < 0.05$.

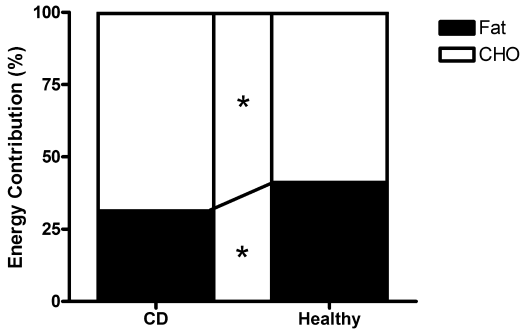

FIGURE 3. Percent of energy expenditure contribution of fat and CHOs in children with CD and controls. Values are averaged over the 4 time points (EX1, EX2, EX3, and EX4) and are expressed as mean percentage. *Significantly different between the groups, $P < 0.05$.

Plasma Glucose

Plasma glucose concentration (reported as mean ± SD in mmol/L) did not change with exercise in children with CD (REST: 4.9 ± 0.6, MID: 4.6 ± 0.6, END: 4.5 ± 1.0). In the controls, plasma glucose decreased from REST (4.6 ± 0.6) at MID (4.0 ± 0.5, $P < 0.05$), whereas plasma glucose at END (4.3 ± 0.5) was similar to REST. There were no significant differences in glucose concentrations between groups.

DISCUSSION

Because of the complete absence of information regarding the effects of exercise on substrate utilization in children with CD, we conducted this study to better understand possible nutritional implications of an active lifestyle for these patients. Our results indicate that during submaximal exercise, children with CD demonstrate lower rates of FAT_{total} oxidation, amount of fat oxidized, and a lower contribution of fat to total EE, when compared with their healthy peers. We are not aware of any published works that have observed substrate utilization in patients with CD during exercise—in either adults or children. That children with CD experienced less reliance on fat oxidation, at least during exercise, indicates an apparent dysregulation in fat metabolism in the face of higher energy demand.

Substrate availability, specifically FFA concentration, has been identified as a major contributor to fat oxidation during submaximal exercise.[22] Given that CD patients and controls demonstrated similar FFA concentrations during exercise, it is unlikely that FFA availability is at the heart of the reduced FAT_{total} oxidation in CD. This, however, does not discount the possibility of impaired FFA uptake, transportation, or oxidation at the level of the skeletal muscle. For example, children with CD have been found to have lower total and free plasma carnitine,[23] an enzyme responsible for the transportation of fatty chains into the mitochondria and the circulating concentrations of which can be indicative of dysfunction in fatty acid oxidation.[24] We did not measure carnitine levels in our patients, although in light of the genetics of CD associated with the IBD5 locus on the fifth chromosome,[25] which coincidentally gives rise to the organic cation/carnitine transporters 1 and 2,[26] future evaluation of the effects of carnitine supplementation on fat oxidation in patients with CD may be warranted.

Differences in fat oxidation between patients and controls may also be related to their state of feeding and medication use. Based on 2 adults studies performed at rest, patients with CD can display similar or lower[27] or higher[12] fat oxidation than controls in the fasted states, whereas in the fed state, patients with CD can have lower[12,27] or similar[27] fat oxidation to controls. Although we only assessed substrate utilization during exercise, all of our participants were tested during the afternoon, at least 3 hours after food consumption, and were not fasted. Because fasting promotes fat oxidation during exercise,[28] it would be interesting to test patients under fasting conditions to determine if fat oxidation during exercise can be enhanced, thereby providing additional insight into the regulation of fat oxidation during exercise. The scant literature suggests that women with CD being treated with steroids exhibit lower fat oxidation at rest.[27] We therefore, investigated whether medication influenced substrate utilization during exercise in our patients. Only 1 of our 7 participants with CD was undergoing steroid therapy at the time of testing. Although this participant did have the lowest rate and lowest absolute amount of fat oxidized, the exclusion of his results from the CD group did not change the between group comparison (data not shown). Notwithstanding the small sample size in this study, corticosteroids are not likely to play a major role in the observed differences, although this possibility needs to be confirmed with a larger sample size. It is more likely that lower fitness levels observed in children with CD (Table 1) contributed to the lower FAT_{total} oxidation when compared with controls because low fitness has previously been linked with reduced FAT_{total} oxidation at rest[29] and during exercise[30] in healthy individuals. Exercise training studies designed to improve fitness are needed in children with CD to determine the effects on fat oxidation at rest and during exercise.

In this study, lower rates of FAT_{total} oxidation and absolute amounts of fat oxidized in CD were not mirrored by exaggerated rates of CHO oxidation. This suggests that those with CD may have normal glucose metabolism during exercise, a finding supported by similar plasma insulin concentrations between children with CD and healthy controls. During exercise, plasma glucose concentrations remained stable in those with CD but decreased in controls, which may indicate an enhanced ability to stabilize plasma glucose concentration given the greater reliance on CHO observed in the patients. From an applied perspective, the greater contribution of CHO to total energy yield in youth with CD compared with controls underscores the importance of replenishing glycogen stores after exercise in this population. This recommendation is in agreement with the current recommended dietary changes in patients with CD because high CHO and low fat diet may be advocated for some patients with CD to reduce inflammation.[31] Although consuming a high CHO diet may seem to be a simple solution for glycogen restoration, this approach requires consideration of the type of carbohydrate consumed. For example, fermentable oligo-, di-, monosaccharides, and polyols are poorly digested

short-chained CHOs that may contribute to functional symptoms such as abdominal bloating, pain, and diarrhea in patients with CD.[32] A diet low in fermentable oligo-, di-, monosaccharides, and polyols has been associated with fewer negative side effects in this population.[33] Future research should investigate the interaction of diet and exercise metabolism in patients with CD. Specifically, it would be interesting to determine whether differences in fat oxidation would be observed between children with CD on a high CHO low fat versus a low CHO high fat diet.

LIMITATIONS

Notwithstanding our novel findings, this study was limited by a relatively small sample size, although the differences we observed were large and robust. Moreover, we cannot discount the possibility that food intake in the previous 24 to 48 hours, which we did not control for, could have influenced substrate utilization during exercise.[17] However, despite the reduction in fat oxidation in our participants, no differences were observed in CHO oxidation; this likely rules out the potential for major dietary differences between the groups in the days before exercise.

It is important to point out that relative exercise intensity during exercise, expressed as $\%\dot{V}O_{2peak}$, was different between the groups. It was for this reason that we used relative intensity as a covariate in our analyses of covariance. Nevertheless, children exercising at a higher relative intensity would be expected to rely on proportionally less fat than CHO. Future studies should assess substrate utilization at different exercise intensities to better understand fat oxidation,[34] because the optimal rate of fat oxidation may occur at different exercise intensities for different individuals.

CONCLUSIONS

We observed altered fat metabolism in children with CD during submaximal exercise. Specifically, children with CD oxidized fat at a lower rate leading to a reduction in the total amount of fat used and less energy yield from fat compared with healthy sex-matched and biological age-matched controls. The observed differences in fat metabolism could not be explained by fuel availability (plasma insulin, FFA, or glucose), which was found to be similar in CD and controls. Furthermore, youth with CD demonstrated a greater energy yield from CHO during exercise suggesting a possible compensatory response. These findings highlight the importance of further investigating optimal diets in this population to support a physically active lifestyle.

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