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Original Article

Reduced fat oxidation rates during submaximal exercise in boys with cystic fibrosis☆

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Abstract

Background: Exercise is a viable form of therapy for children with cystic fibrosis (CF). Understanding the energy sources used during exercise would aid CF patients in obtaining proper nutrition in order to sustain an active lifestyle.
Methods: Six boys with CF (mean age ± SD: 14.8 ± 2.3 yrs, FEV1: 99 ± 18% predicted) and six matched controls (14.0 ± 2.2 yrs) completed a session of two 30 min bouts of cycling at an intensity set at 50% peak mechanical power. Rates of total fat and carbohydrate (CHO) oxidation were calculated from expired gases. Plasma insulin, glucose and free fatty acid (FFA) were determined before, during and at the end of the exercise.
Results: Rates of fat oxidation (expressed in mean mg × kg body weight^{-1} × min^{-1} ± SD) were significantly lower in children with CF (5.7 ± 1.6) compared to controls (8.6 ± 1.8, $p < 0.05$). Children with CF also had lower values than controls in amount of fat oxidized (CF: 17.3 ± 5.0 g, controls: 26.1 ± 5.9 g, $p < 0.05$) and percent of total energy expenditure from fat (CF: 32 ± 6%, controls: 43 ± 7%, $p < .0.05$), but a higher contribution from CHO (CF: 68 ± 6%, controls: 57 ± 7% $p < .0.05$). Plasma FFA was significantly lower in children with CF compared to controls during (CF: 252.5 ± 117.9 μM, controls: 602.2 ± 295.6) and at the end of exercise (CF: 430.9 ± 180.6, controls: 1147.5 ± 473.5). There were no differences in the rates of CHO oxidation, insulin or glucose between groups.
Conclusion: Fat metabolism during exercise is impaired in boys with CF and may be attributed to an inability to mobilize FFA.

Keywords: Substrate utilization; Free fatty acids; Cycling; Cystic fibrosis

1. Introduction

Patients with cystic fibrosis (CF) encounter difficulties with lipid digestion and absorption. Mutations in the CFTR chloride channel in the pancreas inhibit pancreatic lipase and bicarbonate secretion leading to poor lipid digestion and malabsorption of properly digested lipids [1]. Even with pancreatic enzyme replacement therapy, lipid malabsorption is still evident with only 80–90% of lipid ingested being absorbed, whereas normal lipid absorption is ~95% [2]. Due to these issues with lipid absorption, a high lipid diet is promoted for its high caloric density [3] emphasizing the importance of fat as a fuel, and in overall CF nutrition.

Malnutrition is thought to be the primary explanation for impaired growth traditionally observed in CF patients [4]. Whereas impaired growth is only evident in a small proportion

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of children – ~7% of Canadian children with CF are below the 5th percentile for height and ~7% are below the 5th percentile for weight [5] – between 25 and 35% of Canadian adults with CF are considered underweight [5]. These findings suggest that therapeutic intervention strategies should begin during early childhood development.

Exercise is thought to be an excellent form of therapy for the CF population [6], with evidence that greater fitness and physical activity are related to increased chances of survival and a slower decline in pulmonary function, respectively [7–9]. One of the clinical strengths in exercise therapy for CF patients lies in the ability to improve fitness and pulmonary function [6,10–12]. However, there is very little information regarding the impact of exercise on fuel metabolism in children with CF. Since children with CF experience malnutrition that results in alternative dietary requirement in regards to fat, understanding substrate utilization, particularly fat utilization, during exercise would provide valuable information to guide patients with respect to dietary considerations to support an active lifestyle. Greater understanding of substrate utilization during exercise may also inform appropriate nutritional intake contributing to improved growth rates.

Limited research studying substrate utilization during exercise in patients with CF has been conducted and the results are conflicting. One study involving 10 children and young adults has shown no differences between CF patients and controls during exercise [13]. Conversely, two other studies reported a higher proportion of carbohydrates (CHO) oxidized during exercise in a group of CF patients, comprised of both children and young adults or children only [14,15], indicating a greater reliance on CHO utilization rather than fat utilization during exercise. However, all of these studies reported only the respiratory exchange ratio (RER) and did not calculate oxidation rates of fat or carbohydrate to assess substrate utilization. The objectives of this study were to determine (1) whether substrate utilization, in particular the use of fat, during submaximal exercise is altered and (2) the effect of exercise on plasma insulin, glucose and free fatty acids (FFA) in children with CF compared to healthy control children.

2. Methods

2.1. Participants

Six clinically stable males with CF and six control males participated in the study. Children with CF were recruited from the McMaster Pediatric Cystic Fibrosis clinic at the McMaster Children's Hospital. Patients that could not perform reproducible pulmonary function tests were excluded from the study. Recruitment took place during the weekly outpatient pediatric CF clinic. Patients that met the inclusion criteria were approached by the clinic doctor, nurse, physiotherapist, dietitian or child life specialist and asked if they would be interested in hearing about an exercise study. Families who said "yes" were given a detailed synopsis about the study by the research coordinator and asked if they were interested in being contacted further. Families who were interested filled out a consent-to-contact form. From our experience, we found CF patients who were engaged in physical activity or sports were more likely to participate in the study. In the years of recruitment (2008 & 2009), our clinic followed an average of 93 patients annually; 40 of these patients were males and of these, 19 were in the age range of 9 to 17 years. Healthy children with no known chronic illness and not taking any medication were included in the study as controls. Control boys were recruited as friends of a CF patient or from the local community by the use of flyers that were distributed to schools and placed in public areas (e.g., recreation centers and libraries). Children with CF and controls were matched by sex and biological age, as determined by estimated years from the age of peak height velocity (PHV) [16]. The study was approved by the Hamilton Health Science/Faculty of Health Science Research Ethics Board. Consent and assent were obtained from parents/guardian and children, respectively, before induction into the study.

2.2. Experimental design

2.2.1. Visit 1

Visit 1 consisted of standard measures of standing height measured to the nearest 0.1 cm using a calibrated stadiometer and body mass measured to the nearest 0.1 kg using digital scale (BWB-800, Tanita Corporation). A bioelectric impedance analyzer (BIA 101A, RJL system) was used to assess body composition for descriptive purposes only. Fat free mass (FFM) was calculated using an age-specific BIA equation [17] and percent body fat was calculated as [(Body weight − FFM) / body weight] × 100. Pulmonary function (FEV_1) was assessed using the Vmax29 SensorMedics flow volume loop program. Peak mechanical power (PMP) and VO_{2peak} (Vmax29, SensorMedics) were determined using the McMaster All-Out Progressive Continuous Cycling Test on a mechanically braked cycle ergometer (Fleisch–Metabo) as previously described [18].

2.2.2. Visit 2

Visit 2 occurred on a separate day and at least two days after the first visit to avoid residual effects from the previous exercise session. In preparation for this visit participants were asked to: 1) refrain from any food or liquid consumption, except water, for 3 h prior to the visit, 2) refrain from eating foods such as pizza, burgers, French fries, etc, the day before and day of the visit, and 3) not participate in any strenuous physical activity 24 h before the visit. Visit 2 consisted of two 30 min bouts of cycling with 6 min of rest between bouts. The participant cycled at a constant pace of 60 rpm at an intensity set at 50% PMP. Breath-by-breath gas exchange (O_2 and CO_2) was assessed (Vmax29, SensorMedics) for 6 min at 12–18 min (EX1) and at 23–29 min (EX2) of the first 30 min bout of exercise, and at 12–18 min (EX3) and 23–29 min (EX4) of the second 30 min bout of exercise. The last 3 min of each gas collection period was averaged and used for analysis. An indwelling catheter was placed in an arm vein of the participant after 10 min of supine rest before exercise commenced. Blood samples were collected before exercise (REST), at the mid-point of exercise after the first 30 min (MID), and immediately at the end of exercise after the second 30 min (END). Blood samples were processed to extract plasma and stored at −80 °C until analysis.

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2.3. Substrate utilization

Rates of whole body fat and CHO oxidation were calculated using the following equations [19]:

$$FAT_{total}(g/min) = -1.70 \cdot \dot{V}CO_2(1/min) + 1.69 \cdot \dot{V}O_2(1/min)$$
$$CHO_{total}(g/min) = 4.59 \cdot \dot{V}CO_2(1/min) - 3.23 \cdot \dot{V}O_2(1/min).$$

The energy potentials of fat (9.75 kcal/g) and CHO (3.87 kcal/g) were used to calculate energy expenditure (EE) and the energy yield from each macronutrient, and expressed as a percent of EE. The contribution of protein to EE was considered to be negligible compared to that of fat and CHO and was, therefore, ignored. In addition, the amount of fat and CHO oxidized (expressed in grams) was determined using area under the curve (AUC) based on oxidation rates at EX1, EX2, EX3 and EX4.

2.4. Blood analyses

Plasma insulin was analyzed using commercially available enzyme-linked immunosorbant assay (ELISA) kits (Invitrogen Corporation). Plasma glucose was analyzed using assay colorimetric kits (Cayman Chemical Company). Plasma free fatty acids were analyzed using ELISA kits (BioZen, Inc.). The coefficient of variation for insulin, glucose and FFA was 3.1%, 2.8% and 4.1%, respectively. All exercise values were adjusted for changes in plasma volume [20].

2.5. Statistical analysis

Data were tested for normal distribution using Shapiro–Wilk test (SPSS version 17.0, $p < 0.05$). Height percentiles were not normally distributed and were analyzed using a Mann–Whitney *U* test ($p < 0.05$). Age, estimated years from PHV, weight percentiles, % body fat, VO_{2peak}, FEV_1, and relative intensity were normally distributed and compared between groups using an independent *t*-test ($p < 0.05$). Fat and CHO oxidation rates, grams oxidized, % of total EE, glucose and FFA were normally distributed, while insulin values were not normally distributed. Insulin values were log transformed to achieve normal distribution and log values used for analyses. EE and grams of fat and CHO oxidation were compared between groups using an independent *t*-test. One-way repeated measure ANOVAs (Statistica version 5.0, $p < 0.05$) were performed on FAT_{total}, CHO_{total}, % fat of total EE, % CHO of total EE, insulin, glucose and FFA concentrations separately for children with CF and controls to determine the effect of exercise. Two-way repeated measure ANOVAs were performed on the same variable as in the one-way ANOVA analyses to determine group differences. The two factors examined were group (two levels: CF, Control) × time (four levels: EX1, EX2, EX3, EX4 or three levels: REST, MID, END, depending on variable). If a main effect for group and/or a group × time interaction was present, Tukey's HSD post hoc analyses were performed to test for differences between means. Significance was set at $p \leq 0.05$. Values are expressed as mean ± SD, unless stated otherwise. Effect sizes were determined for any significant differences between children with CF and controls using means, pooled standard deviations (SD) and the following equation: Effect size = (Mean of control group − Mean of CF group) / SD_{pooled}.

3. Results

3.1. Participants

Participant characteristics are presented in Table 1. There were no significant differences between groups in any of the characteristic variables, except for VO_{2peak}. Children with CF were less fit than the control group. Both groups were working at the same relative intensity during the experimental session.

3.2. Oxidation rates

In children with CF, FAT_{total} oxidation rates (expressed in mean mg × kg body weight^{-1} × min^{-1} ± SD) at EX3 (6.3 ± 2.1, $p < 0.05$) and at EX4 (6.8 ± 1.8, $p < 0.05$) were higher than at EX1 (4.5 ± 1.3) (Fig. 1.A). FAT_{total} at EX2 (5.4 ± 2.0) and at EX1 were similar in children with CF. In healthy controls, FAT_{total} oxidation rates at EX2 (8.7 ± 2.9, $p < 0.01$), EX3 (9.2 ± 2.2, $p < 0.01$) and EX4 (10.7 ± 1.4, $p < 0.001$) were higher than at EX1 (5.9 ± 1.7) (Fig. 1.A). Children with CF had a significantly lower average rate of FAT_{total} oxidation compared to controls (CF: 5.7 ± 1.6, controls: 8.6 ± 1.8, $p < 0.05$) (Fig. 1.C), and oxidized a lower amount of fat (AUC) compared to controls (CF: 17.3 ± 5.0 g, controls: 26.1 ± 5.9 g, $p < 0.05$) (Fig. 1.E). The effect sizes between the two groups for fat oxidation rate and fat oxidized were 1.32 and 1.26, respectively. CHO_{total} oxidation rates (expressed in mean mg × kg body weight^{-1} × min^{-1} ± SD) did not change during exercise for children with CF (EX1: 32.6 ± 4.8, EX2: 31.6 ± 4.0, EX3: 30.5 ± 4.0, EX4: 29.6 ± 7.2), while in controls, values at EX4 (23.7 ± 1.5) were lower than at EX1 (32.9 ± 5.0, $p < 0.01$) (Fig. 1.B). There was no difference in the average oxidation rate of CHO_{total} between children with CF and controls (CF: 31.1 ± 3.8, controls: 28.3 ± 3.2) (Fig. 1.D) or in the

Table 1
Participants' characteristics.

	CF (n = 6)	Controls (n = 6)	P values
Age	14.8 ± 2.3	14.0 ± 2.2	0.545
Age range	(11.4–17.1)	(10.0–16.2)	
Estimated years from PHV	0.6 ± 2.0	0.6 ± 2.1	0.989
Height percentile	45.9 ± 25.9	80.2 ± 19.3	0.065
Weight percentile	45.9 ± 20.1	62.3 ± 22.1	0.212
Body fat (%)	19.3 ± 6.2	16.2 ± 8.4[†]	0.492
VO_{2peak} (ml/kg/min)*	50.3 ± 3.8	54.9 ± 3.0	0.046
FEV_1 (% predicted)	99 ± 18	101 ± 13	0.489
Relative intensity (%)	61.7 ± 3.0	62.8 ± 4.9	0.665

Values are expressed in mean ± SD. CF: Cystic fibrosis, PHV: Peak height velocity, VO_{2peak}: peak oxygen consumption, FEV_1; Force expiratory volume in 1 s. *Significant difference between groups. [†]n = 5. Height and weight percentile reference values were obtained from Stature-for-age and Weight-for-age data files from the Centre and Disease Control [28], respectively. Percent body fat was calculated using an age-specific BIA equation from Schaefer et al. [17]. Percent FEV_1 predicted were calculated using reference values based on age- and height-specific equation from Wang et al. [29].

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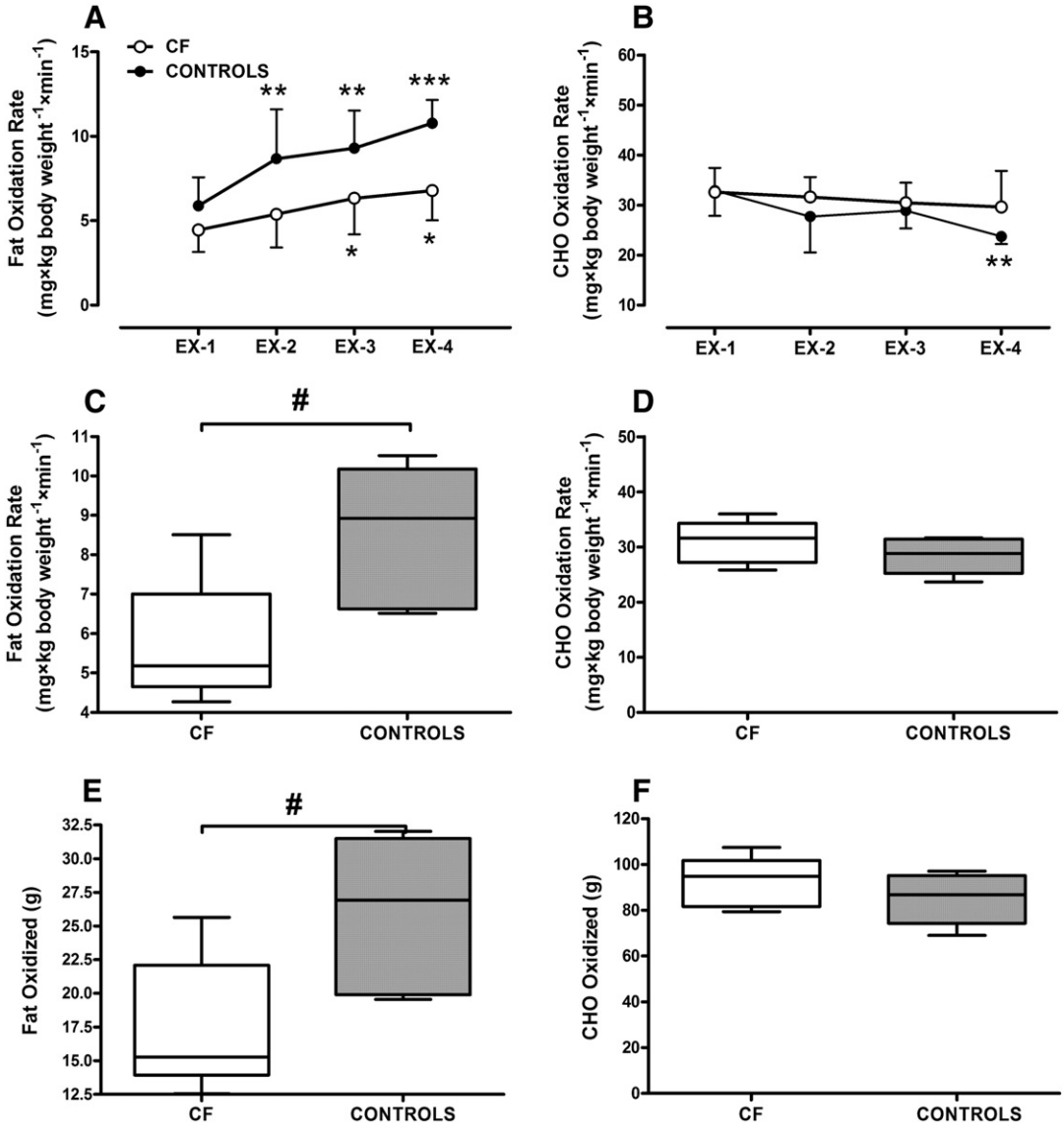

Fig. 1. (A) Fat oxidation rates. (B) Carbohydrate oxidation rates. (C) Average fat oxidation rates (D) Average carbohydrate oxidation rates. (E) Amount of fat oxidized. (F) Amount of carbohydrates oxidized. Values are expressed in mean ± SD for graphs A and B. Values are expressed in median, 25th and 27th percentile, and range for graphs C–F. CF: Cystic fibrosis. Amount of substrate oxidized was determined using area under the curve. Significantly different from rest: *$p < 0.05$, **$p < 0.01$. ***$p < 0.001$. Significantly different between groups, #$p < 0.05$.

amount of CHO oxidized (CF: 93.2 ± 10.7 g, controls: 85.1 ± 10.9 g) (Fig. 1.F).

3.3. Energy yield

In children with CF, the average EE was 566 ± 160 kcal. In controls, the average EE was 624 ± 162 kcal. We also compared EE normalized to both FFM and body weight. Because body composition (i.e., % body fat) was similar between the groups these comparisons gave identical results. Therefore, we report EE normalized to body weight to maintain consistency with substrate data. Values were not significantly different ($p = 0.30$) between groups (CF: 11.2 ± 1.0 kcal/kg body weight vs. controls: 11.2 ± 1.3 kcal/kg body weight). In children with CF, the percent of EE from FAT_{total} at EX4 (37 ± 9%, $p < 0.05$) was higher than at EX1 (26 ± 7%), while values at EX2 (30 ± 10%) and EX3 (34 ± 10%) were similar to EX1. In controls, the percent of EE from FAT_{total} at EX2 (44 ± 15%, $p < 0.05$), EX3 (44 ± 9%, $p < 0.05$), and EX4 (53 ± 2, $p < 0.001$) were higher than at EX1 (31 ± 9%). In children with CF, the percent of EE from CHO_{total} to EE at EX4 (63 ± 9%, $p < 0.05$) was lower than at EX1 (74 ± 7%), while values at EX2 (70 ± 10%) and EX3 (66 ± 10%) were similar to EX1. In controls, CHO_{total} contribution to EE significantly decreased at EX2 (56 ± 15%, $p < 0.05$), EX3 (56 ± 9%, $p < 0.05$), EX4 (47 ± 2, $p < 0.001$), compared to EX1 (69 ± 9%). Between groups, children with CF relied significantly less on FAT_{total} (CF: 32 ± 7%, $p < .0.05$) and more on CHO_{total} (CF: 68 ± 7%, $p < .0.05$) compared to controls (fat: 43 ± 7%, CHO: 57 ± 7%) (Fig. 2). The effect size for FAT_{total} and CHO_{total} contribution to EE was 1.25 for both variables. The median, 25th and 75th percentiles, and ranges for the CHO_{total} contribution to EE for children with CF and controls were 68.4,

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64.5 and 74.9 (56.4–75.1) and 56.7, 49.2 and 65.0 (48.4–65.6), respectively. The median, 25th and 75th percentiles, and ranges for the FAT_{total} contribution to EE for children with CF and controls were 31.6, 25.0 and 35.5 (24.9–43.6) and 43.2, 34.9 and 50.7 (34.5–51.6), respectively.

3.4. Blood analysis

Insulin — In children with CF, the insulin concentration at MID ($p < 0.05$) and END ($p < 0.01$) was lower than at REST ($p < 0.05$ and $p < 0.01$, respectively), while there was no effect of exercise on insulin concentrations in controls (Table 2). There were no differences between groups in insulin concentrations.

Glucose — In children with CF, the glucose concentration did not change with exercise. In contrast, in controls the concentration at MID ($p < 0.05$) was lower than at REST ($p < .05$) while concentrations at REST and END were similar (Table 2). There was no significant difference in glucose concentration between groups.

Free fatty acid — In children with CF, FFA concentrations at END (430.9 ± 180.6) were higher than at REST (197.5 ± 89.6 μM, $p < 0.01$), while concentrations at MID (252.5 ± 117.9) and REST were similar (Fig. 3). Similarly, FFA concentrations at END (1147.5 ± 473.5, $p < 0.001$) in controls were higher than at REST (369.1 ± 178.3 μM), while concentrations at MID (602.2 ± 295.6) were not different from REST. Between children with CF and controls, REST concentrations were not significantly different. However, children with CF had significantly lower FFA concentrations at MID ($p < 0.05$) and at END ($p < 0.001$) of exercise compared to controls (Fig. 3). The effect sizes at MID and at END were 1.24 and 1.41, respectively.

Table 2
Plasma insulin and glucose concentrations before and during exercise in children with CF and controls.

	REST	MID	END
Insulin (pmol/l)			
CF	139.1 (90.7–213.3)	85.5 (65.6–111.3)*	82.0 (64.3–104.5)**
Controls	97.5 (72.9–130.4)	69.1 (45.3–105.3)	82.2 (56.2–120.1)
Glucose (mmol/l)			
CF	4.6 ± 0.8	4.1 ± 0.4	4.0 ± 0.5
Controls	4.7 ± 0.5	4.0 ± 0.5*	4.5 ± 0.4

Insulin values are expressed in geometric mean (95% CI). Glucose values are expressed in mean ± SD. REST: before exercise, MID: mid-way of exercise, END: end of exercise, CF: Cystic fibrosis. Significantly different from rest: *$p < 0.05$, **$p < 0.01$. There were no differences between groups.

4. Discussion

The results of the current study suggest that children with CF have altered fat metabolism during submaximal exercise. Despite our small sample size, the effect sizes were large. Even in our patients who were quite healthy, they demonstrated a lower rate of fat oxidation, lower amount of fat oxidized and a lower percentage of fat derived EE, compared to healthy controls. To our knowledge, this is the first study to examine whole body oxidation rates of fat and CHO during prolonged submaximal exercise in children with CF. Two prior studies examined substrate utilization in CF patients comprised of both children and young adults making it impossible to know the results specific to the pediatric group; these studies gave conflicting results [13,14]. Wideman et al. [13] tested 10 CF patients aged 10–22 years who, compared to controls, had similar RER, indicating a similar balance in the oxidation of fat and CHO during 20 min of submaximal exercise performed at 50% of their VO_{2peak}. Conversely, Spicher et al. [14] reported that 13 patients with CF, aged 8–24 years, had similar RQ (term used by authors) values after ~10 and ~20 min of exercise but greater RQ values after ~30 min of submaximal incremental exercise compared to controls, indicating higher oxidation of CHO relative to fat. Recently Bongers et al. [15], who tested only patients within the pediatric age range, also reported higher RER values at the end of maximal exercise in 22 patients (age range of 11–18 years) compared to healthy peers. Our results are in agreement with the findings of Spicher et al. [14] and Bongers et al. [15]. It may be possible that differences in substrate oxidation in CF patients become more apparent during exercise lasting 30 min or longer or with incremental exercise. It is also important to note that the average EE during exercise was not different between our groups, so this cannot account for the difference in substrate utilization.

Participants with CF in the current study enjoyed high fitness levels, although slightly lower than controls. Given the importance of aerobic fitness as a determinant of fat oxidation

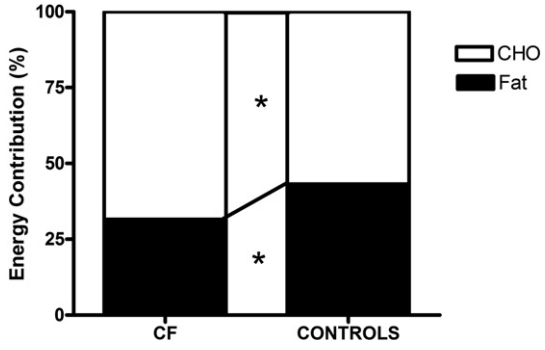

Fig. 2. Percent of energy expenditure contribution of fat and carbohydrates in children with CF and controls. Values are averages over the 4 three time points and are expressed as mean. CF: Cystic fibrosis, CHO: Carbohydrate. *Significantly different between groups, $p < 0.05$.

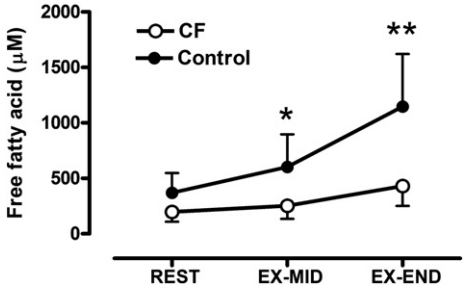

Fig. 3. Plasma free fatty acids in children with CF and controls. Values are expressed in mean ± SD CF: Cystic fibrosis. REST: before exercise, MID: mid-way of exercise, END: end of exercise, Significantly different between groups at the specific time point indicated: *$p < 0.05$, **$p < 0.001$.

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[21] we performed an ANCOVA analysis accounting for VO_{2peak} (data not shown) and confirmed a significant difference between the CF and controls in fat oxidation. The use of steroids by CF patients may also play a role in altered fat metabolism. In fact, women with Crohn's disease, a chronic inflammatory bowel disease, using steroids display lower resting fat oxidation compared to their healthy peers [22]. In our study, two of the six children with CF were on inhaled steroids. Re-analysis of the data with only patients not on steroids resulted in the same difference in fat oxidation rate and FFA (data not shown), ruling out the use of steroids as a possible reason for the differences observed. However, we acknowledge that the small sample size (n = 4) is a limitation in drawing a firm conclusion with respect to steroid use. It is also worth mentioning that these data are taken only from boys and data from girls with CF are needed.

In this study, we also found that the lower rates of fat oxidation were mirrored by lower plasma FFA concentrations during exercise. Less FFA mobilization at higher energy demand may help explain the observed lower rates of fat oxidation in children with CF. An influx of FFA to the blood during exercise is attributed to the hormonal stimulation [23] of triglycerol hydrolysis in adipose tissue [24]. This may suggest either an impaired lipolysis stimulation, impaired rate of lipid hydrolysis, or impairment in the translocation of FFA from intracellular to extracellular compartments during exercise in children with CF. Given no differences in percentage body fat (as measured by BIA) between our two groups, it is unlikely that endogenous fat reserves were a limiting factor in FFA mobilization.

Insulin plays a regulatory role in lipolysis [25]. A decrease in insulin is required for the promotion of the breakdown of triglycerides to FFA and occurs during the first 30–40 min of exercise [26]. We found no differences between groups, but did observe a decrease in insulin values during exercise from resting levels in the CF group. Therefore, insulin is not likely to explain the altered metabolism observed during exercise in our CF participants.

Children with CF are at risk for developing impaired glucose metabolism and cystic-fibrosis-related diabetes due to the loss of pancreatic beta cell function or cell death, and consequently reduced insulin secretion [27]. In the current study, the concentration of glucose, rates of CHO oxidation and amount of CHO oxidized observed in children with CF and controls were similar. During prolonged exercise, fat is the favored substrate over CHO [26]. In our control participants, the rate of CHO oxidation decreased from EX1 to EX4, but this normal response was not observed in children with CF. Children with CF may need to maintain high rates of CHO oxidation during exercise to compensate for an inability to use fat as a fuel.

5. Conclusion

Disease-related differences in exercise metabolism are important for patients and clinicians to consider in the context of appropriate nutritional intake to support an active lifestyle. Our results indicate that for prolonged submaximal exercise, children with CF can maintain their reliance on CHO as a fuel source, but fail to upregulate FFA utilization to a similar extent as healthy children. Determining the mechanisms for this impaired fat metabolism during exercise is beyond the scope of this study; however, the lower plasma FFA found in CF participants may indicate impairment in the mobilization of FFA. Given the differences in metabolism during exercise, additional research is needed to better understand substrate partitioning during exercise, including protein utilization, and nutritional requirements of patients to sustain a healthy active lifestyle.

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