Combined Exercise Training Improves Glycemic Control in Adult with Cystic Fibrosis

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ABSTRACT

BEAUDOIN, N., G. F. BOUVET, A. CORIATI, R. RABASA-LHORET, and Y. BERTHIAUME. Combined Exercise Training Improves Glycemic Control in Adult with Cystic Fibrosis. *Med. Sci. Sports Exerc.*, Vol. 49, No. 2, pp. 231–237, 2017. **Purpose**: Glucose abnormality and diabetes are the most common comorbidities in cystic fibrosis (CF). Combined (aerobic and resistance) exercise program in type 2 patients with diabetes demonstrated an improvement of glycemic control. The aim of the study was to determine whether a combined exercise program is beneficial to improve plasma glucose at 2 h of the oral glucose tolerance test in CF. **Method**: Eighteen adults with CF with glucose abnormality were recruited (Clinicaltrial.gov: NTC02127957), and 17 were randomly assigned to a control or exercise group for 12 wk. $\dot{V}O_{2max}$, oral glucose tolerance test, muscular endurance and strength, and quality of life were measured pre- and postintervention. **Results**: Fourteen participants completed the protocol. Patients in the exercise group improved significantly their 2-h plasma glucose values (-2.34 ± 1.26 mmol·L^{-1}, $P < 0.007$, confidence interval = 99.22%) and presented a reduction of 17.2% ($P < 0.05$) in total glucose excursion. No significant change for other parameters was observed. **Conclusion**: A combined exercise program improves glycemic control in CF. **Key Words:** CYSTIC FIBROSIS–RELATED DIABETES, TRAINING, GLUCOSE TOLERANCE, DYSGLYCEMIA

Cystic fibrosis (CF) is the most common lethal autosomal recessive disease among Caucasians (6). Improvement in life expectancy in patients with CF is associated with the emergence of secondary complications such as CF-related diabetes (CFRD). CFRD is the most common comorbidity in CF, and its prevalence is evolving along with the improved survival of patients with CF: 20% of adolescents and 40%–50% of adults develop CFRD (22). CFRD occurrence is associated with a poor nutritional status, premature decline in lung function, increase in pulmonary infections, and microvascular complications (e.g., retinopathy) (20). The presence of CFRD in patients with CF increases their risk of morbidity and mortality (22).

CFRD is mainly due to reduced insulin secretion, but the effect of additional factors including reduced insulin sensitivity is plausible (7,9). CFRD is preceded by a long phase of prediabetes, a period characterized by an accelerated decline in lung function and body weight as compared with patients who do not develop CFRD (13). The cause of this accelerated decline is yet to be established, but the roles of increased glucose excursions and reduced insulin secretion are suspected (8,13).

Indeed, insulin insufficiency, independently of its effect on blood glucose levels, has a negative effect on nutritional status of patients with CF by increasing protein catabolism and thus favoring weight loss (21). In addition, repeated glucose excursions could promote lung infection, inflammation, and oxidative stress (5,9).

In the general population, it is well established that exercise plays a role in the prevention of type 2 diabetes (T2D) (1,33) and improves glycemic control (1,29) mainly through its positive effect on insulin sensitivity (33). Several studies have reported the benefits of a combined aerobic and resistance exercise program (CEP) for patients with prediabetes (17) or T2D on glycemic control (as judged by the glycated hemoglobin [29]) and on 2 h of oral glucose tolerance test (OGTT) plasma glucose (31), insulin sensitivity (31), and inflammation (16).

Exercise training is already part of regular outpatient care offered to most patients with CF with demonstrated benefits in most but not all studies for maximal aerobic exercise capacity, pulmonary function, and quality of life (QoL) (19,27). The effect of a training program for patients with CF with abnormal glucose tolerance profile has not yet been explored.

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The aim of our study was to investigate if 12 wk of a CEP would improve plasma glucose during an OGTT. The primary objective was to demonstrate an improvement of 2-h OGTT glucose value, the key value that establishes CF glucose tolerance category (11). Our hypothesis was that a CEP would improve abnormal glucose tolerance as well as glycemic control in patients with CF. Because glucose tolerance improvement with exercise training could be mediated by insulin sensitivity and/or secretion as well as on inflammatory and cytokine profiles, these parameters were also investigated as exploratory measures.

MATERIALS AND METHODS

Subject

Adult with CF (>18 yr) were recruited in a randomly assigned open label study with two parallel arms (exercise and control group) between August 2013 and November 2014 at the CF clinic of the Centre Hospitalier de l'Universite de Montreal (CHUM). Randomization was conducted in block by gender with a ratio of 2:2. The protocol was approved by the Institutional Review Board of the CHUM and the Institut de Recherches Cliniques de Montreal. A written informed consent was obtained before data collection. Inclusion criteria were 1) sedentary (less than 100 min·wk^{-1} of structured exercise, assessed by physical activity questionnaire and phone interview), 2) forced expiratory volume in 1 s (FEV_1) >40%, 3) clinically stable for the last 6 wk, and 4) abnormal glucose tolerance (impaired glucose tolerance [IGT], CFRD without pharmacological treatment for diabetes, or elevated 1-h plasma glucose at the OGTT (indeterminate, 1-h OGTT >11.0 but 2-h OGTT <7.8 mmol·L^{-1} [INDET]). Exclusion criteria were 1) current pulmonary exacerbation, 2) use of oral or intravenous corticosteroid, 3) known of low saturation (SpO_2) during exercise, and 4) history of hemoptysis in the last 6 wk. Information is available on Clinicaltrial.gov (NTC02127957).

Assessments

Participation in the study involved six visits (V) (V1: OGTT, one-repetition maximum [1RM] testing, FEV_1, dual-energy x-ray absorptiometry [DEXA], blood work, questionnaire, and physical activity monitor (SenseWear Armband); V2: cardiopulmonary exercise testing [CPET] and supervised training session; V3: supervised training session; V4: supervised training session; V5: OGTT, 1RM testing, FEV_1, DEXA, blood work, questionnaire, and SWA; and V6: CPET) and eight phone calls for the exercise group and four visits (V1: OGTT, 1RM testing, FEV_1, DEXA, blood work, questionnaire, and SWA; V2: CPET and physical activity counseling; V3: OGTT, 1RM testing, FEV_1, DEXA, blood work, questionnaire, and SWA; and V4: CPET) and two phone calls for the control group. The four following evaluations were administered before and after the 12-wk protocol.

OGTT. After an overnight fast, all subjects came to the Institut de Recherches Cliniques de Montreal and underwent a 2-h OGTT. They ingested in less than 5 min a glucose solution: 1.75 g·kg^{-1} of body weight with a maximum of 75 g according to the guidelines of the Canadian Diabetes Association (11). Blood samples were drawn at 0, 30, 60, 90, and 120 min to measure plasma glucose and insulin concentrations. Using the American Diabetes Association criteria (20), patients were categorized as having abnormal glucose tolerance (INDET, IGT with 2-h plasma glucose between 7.8 and 11.1 mmol·L^{-1}, and CFRD with 2-h plasma glucose >11.1 mmol·L^{-1}).

After blood was drawn, plasma glucose level was measured immediately in duplicate with a glucose analyzer (YSI 2300 STAT plus, glucose, and lactate analyzer; SI Inc., Yellow Spring, OH). Insulin and inflammatory marker samples were kept frozen at −80°C until analysis. Insulin concentration was measured in duplicate using human insulin radioimmunoassay (Linco Research, Inc., St. Charles, MO). We used insulin and glucose values during the OGTT to evaluate insulin secretion and sensitivity. We used the index proposed by Stumvoll et al. (14,30)[1] to measure insulin sensitivity, whereas the area under the curve (AUC) values were used to calculate total first and second phase insulin secretion as well as total glucose excursion.

Clinical data. Body weight and height were measured (light clothing and shoes removed), and percent body fat and fat-free mass (kg) were assessed using DEXA (Lunar Prodigy iDXA system; General Electric Lunar Corporation, Madison, WI). Pulmonary function was measured using the American Thoracic Society Standards and FEV_1 (L·s^{-1}), and the predicted % FEV_1 was calculated using Nhanes III equation (Medgraphic 1870, St. Paul, MN). CPET was performed using a graded exercise test on an ergocycle, Ergoline 900 (Bitz, Germany), until voluntary exhaustion, and power output was increased by 5 to 15 W every minute. During the CPET, expired gas samples were analyzed through a mixing chamber, and data were acquired breath by breath with 30 s time averaging, using a Moxus (AEI Technologies Inc., Naperville, IL) cardiorespiratory exercise test station. The highest 30-s average of oxygen uptake value obtained during the exercise test was considered as $\dot{V}O_{2peak}$. Heart rate and SpO_2 were monitored continuously using a 12-lead ECG (Nasiff Associate Inc., New York, NY) and a portable pulse oximetry (Model 8000AA-WO; Nonin Medical, Inc., Plymouth, MN), respectively. Arterial blood pressure was recorded manually at rest and then every 2 min during the CPET. The muscular strength of the leg, pectoral, back, and biceps were measured with the 1RM testing method. Strength was recorded as the maximal weight lifted in one full range of motion, and the 1RM was determined after four trials. Two questionnaires (QoL Cystic Fibrosis Questionnaire-Revised [CFQ-R] [26] and physical activity, http://www.ircm.qc.ca/CLINIQUE/educoeur/Documents/questionnaire.pdf, p. 4) were administered before and after the 12 wk of protocol. The

[1]0.156 − 0.0000459 × (insulin T120 × 6.945) − 0.000321 × (insulin T0 × 6.945) − 0.00541 × glycemia T120.

score of physical activity questionnaire was reported in percent. The questionnaire includes 14 questions, and each question was giving 1 to 4 points (1 = never, 2 = sometimes, 3 = often, and 4 = always) by the subject. A maximum of 56 points were possible, and the addition of the results divided by 56 gives us the score in the percentage of physical activity practice.

Inflammatory biomarkers and cytokine serum levels. Blood samples were used to quantify inflammatory marker concentrations. Interleukin 1β (IL-1β, AL220C), IL-6 (AL223C), and IL-8 (AL224C) were measured in duplicate using a commercial sandwich alpha technique-linked immunosorbent assay kit (alphaLISA assay; Perkin Elmer, Wellesley, MA) according to the manufacturer's instructions, with the exception that the antibody incubation was conducted overnight. YKL-40 protein level was quantified in duplicate using a commercial ELISA kit (DuoSet ELISA; R&D Systems, Minneapolis, MN) according to manufacturer's protocol. C-reactive protein high sensitivity was quantified by a turbidimetric assay of antibody coupled to the in a Cobas Integra® 400 plus analyzer (Roche Diagnostics LTD, Indianapolis, IN).

Physical activity monitoring. Participants wore a physical activity monitor, the SenseWear Armband Pro 3 (SWA; BodyMedia, Pittsburgh, PA), for 5 d, preintervention (before CEP) and postintervention, before the last training session. The SWA was worn on the upper right arm (on the triceps at the midhumerus point). The SWA captures data to calculate energy expenditure through a two-axis accelerometer and heat flux, galvanic skin response, skin temperature, and near-body ambient temperature sensors (Innerview Research Software version 7.1 developed by the manufacturer). SWA was previously validated for the CF population (10) and also against doubly labeled water for healthy adults (4).

Training Program

Subjects were instructed to do the aerobic and resistance training on the same day, 3 $d \cdot wk^{-1}$ with a day off between each training session. Participants record their training session in a diary. Patients were instructed to use the modified Borg scale to adjust training intensity and to quantify dyspnea and fatigue. Once every 4 wk, participants from the exercise group underwent a supervised training session and received a phone call once a week to answer questions, to adjust their exercise, and to confirm that they completed their diary and exercise training forms. Each training session ended with few stretching exercises. Compliance was assessed using recording training session on training sheet and diaries from each subject. A total of 36 training sessions was supposed to be performed for 12 wk. The ratio of training session completed on the 36 training sessions gives us the percentage of compliance for each subject.

Aerobic Training

Aerobic exercise consisted of walking, jogging, cycling, or elliptical trainer. Each session lasted 20 to 40 min (including warm-up and cool down). Training intensity was set at 60% of $\dot{V}O_{2peak}$ achieved during CPET, during weeks 0 to 4. Thereafter, intensity was increased every 4 wk (70%, week 4; 80%, week 8).

Resistance Training

Resistance training program consisted of five to seven exercises for large muscle groups (quadriceps, pectoral, etc.). All subjects performed one to two sets of 8 to 12 repetitions, with a weight of 30%–50% of 1RM. The rest period between sets lasted 60 s. Exercises were adjusted every 4 wk, and subjects were instructed to progressively increase up to three sets of 12 to 15 repetitions. Subjects used free weights, elastic, or body weight to execute their exercises.

Statistical Analysis

Our primary objective was to observe a decrease of 1.5 $mmol \cdot L^{-1}$ of plasma glucose at 2 h of OGTT. This objective is similar to what has been achieved in previous exercise study in type II diabetes (31). To achieve a power of 80% ($P < 0.05$) and to reject the null hypothesis, two groups of nine subjects were needed (GraphPad StatMate, version 2; GraphPad Software Inc., La Jolla, CA). Considering the potential dropout from the study, this meant that 18 to 24 patients would need to be recruited.

Results are expressed as mean ± SD or SEM. Statistical analysis was performed using statistical software GraphPad Prism, version 6 (GraphPad Software Inc.). An Agostino and Pearson standardization test was used, and on the basis of the results, a Wilcoxon signed rank test (nonparametric) was used to evaluate the pre and postdifference in each groups. In addition, the changes overtime in plasma glucose and insulin levels for the test performed before and after the training period were analyzed by a two-way ANOVA. A Bonferroni *post hoc* test was used to identify group differences at each time points, with 95% interval confidence. A value of $P \leq 0.05$ was considered as statistically significant.

RESULTS

Eighteen patients with CF were recruited and 17 were randomized in the study. One patient could not be randomized because of an adverse event (a significant decrease in the blood pressure) during the CPET at screening. During the study, two patients dropped out of the study because of pulmonary exacerbations, and one patient was excluded from the analysis because he was noncompliant to the exercise program (self-reported and information obtained from the diary). Characteristics of the remaining patients ($n = 14$) are presented in Table 1. Participants were categorized as INDET ($n = 2$), IGT ($n = 11$), and CFRD ($n = 2$). Patients randomized to both groups were comparable in terms of FEV_1, cardiorespiratory function, body mass index, age, pancreatic function, and glucose tolerance status (Table 1). The exercise regimen was well tolerated (no reported musculoskeletal

TABLE 1. Participants baseline characteristics (n = 14).

	Exercise Group	Control Group
N	8	6
Age (yr)	31.9 (24; 41)	35.5 (22; 57)
Sex (M/F)	3/5	3/3
Weight (kg)	65.3 (50.4; 85.3)	65.9 (48.2; 82.7)
BMI ($kg \cdot m^{-2}$)	23.3 (20.2; 30.2)	24.1 (20.6; 27.2)
FEV_1 (%)	70.5 (51; 87)	73.2 (52; 95)
$\dot{V}O_{2max}$ ($mL \cdot kg^{-1} \cdot min^{-1}$)	24.29 (14.9; 32.8)	22.98 (14.5; 31.1)
dF508 homozygous/heterozygous/other	3/3/2	3/3/0
INDET/IGT/CFRD	1/5/2	1/5/0
Pancreatic function: PI/PS	7/1	4/2

BMI, body mass index; INDET, indeterminate glycemia at the first hour of OGTT; PI, pancreatic insufficient; PS, pancreatic sufficient.

pain and compliance to the exercise program, as determine from the diary was >80%).

Glucose and insulin response to OGTT. After 12 wk of CEP, the 2-h OGTT plasma glucose was reduced by -2.34 ± 1.26 $mmol \cdot L^{-1}$ ($P < 0.01$) in the exercise group while it remained stable in the control group ($P = 0.69$). We also observed a significant decrease ($P < 0.05$) of the plasma glucose at 1-h OGTT in the exercise group (Fig. 1). The overall glucose excursion as measured by the glucose AUC decreases by 17.2% ($P < 0.02$) in the exercise group, while this parameter remained stable in the control group ($P = 0.84$) (Table 2). There was no significant change in the plasma insulin levels during OGTT in the control or exercise group (Fig. 1). Furthermore, there is no significant change of the total insulin secretion during the OGTT in both groups (Table 2). However, insulin sensitivity increased in the exercise group (+0.016, $P < 0.05$), whereas no change was seen in the control group (Table 2).

Inflammatory biomarkers and cytokine serum levels. No significant change in cytokine or inflammatory biomarker levels was observed, except for YKL-40 (Table 2). YKL-40 protein levels were significantly increased (+41.3 $ng \cdot mL^{-1}$, $P < 0.05$) in the exercise group, whereas YKL-40 remains stable in the control group (Table 2).

Exercise capacity and muscular strength. A significant improvement for the score of physical activity questionnaire was observed in the exercise group (+11.57%, $P < 0.01$). Significant improvements in muscular strength for leg press (+33.3 kg, $P < 0.02$) and sited bench press (+6.8 kg, $P < 0.05$) were observed in the exercise group. However, there was no significant improvement for the lat pulldown ($P = 0.15$) or biceps curls ($P = 0.20$) (see Table, Supplemental Digital Content 1, Anthropometric and physical activity characteristics, http://links.lww.com/MSS/A762).

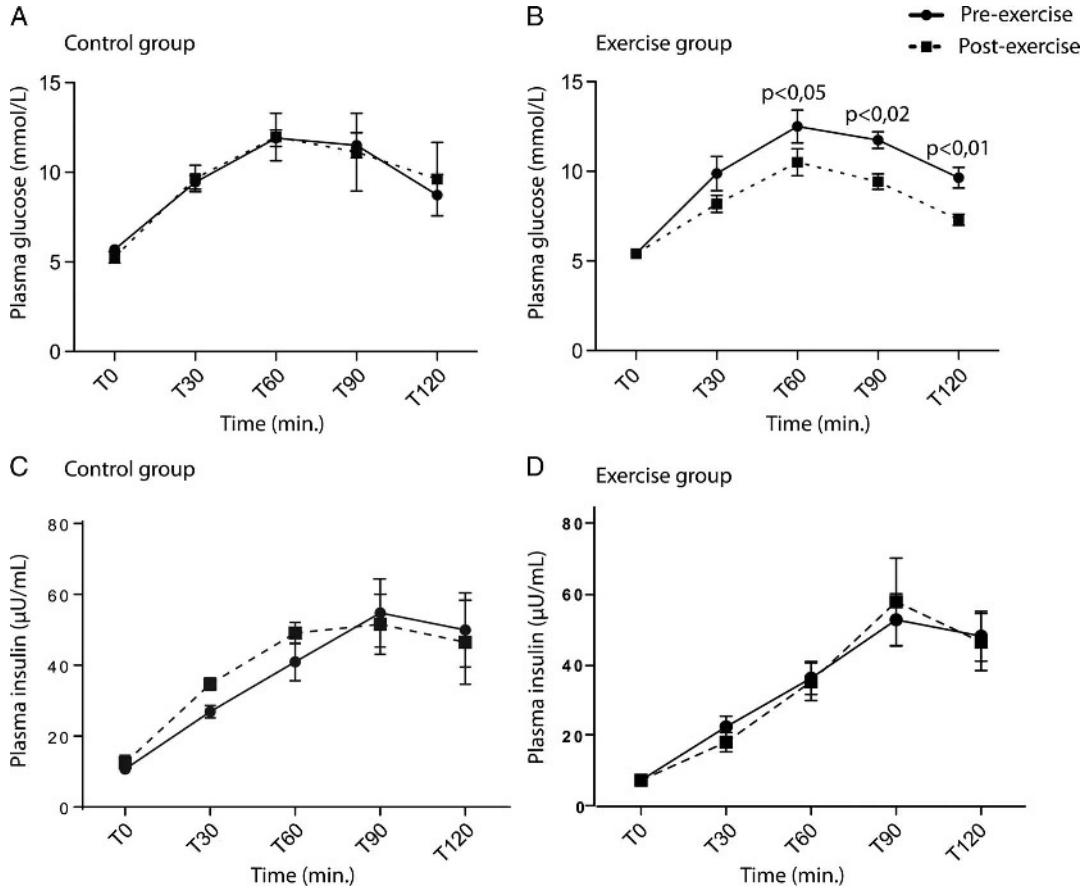

FIGURE 1—Plasma glucose and insulin excursions during an OGTT before (●) and after (■) exercise training program. Plasma glucose levels after 12 wk of training in control group (A) and exercise group (B). Plasma insulin levels after 12 wk of training in control group (C) and exercise group (D). Mean and SEM are presented. The data were analyzed by a two-way ANOVA. There was a significant decrease in plasma glucose during the OGTT after 12 wk of training in the exercise group ($P < 0.002$) but no significant changes in the control group ($P > 0.93$). *Post hoc* analysis with *t*-test has shown a significant difference at time 60, 90, and 120 min as identified in the figure.

TABLE 2. Effect of intervention on metabolic and inflammatory parameters.

	Exercise Group			Control Group		
	Baseline	12 wk	*P*	Baseline	12 wk	*P*
Metabolic parameters						
HbA1c (%)	5.8 ± 0.3	5.7 ± 0.3	0.16	5.7 ± 0.3	5.7 ± 0.4	0.25
Glucose AUC	41.25 ± 5.83	34.47 ± 4.23	**0.02***	40.07 ± 3.92	40.20 ± 11.96	0.84
Insulin sensitivity index	0.069 ± 0.009	0.085 ± 0.01	**<0.05***	0.069 ± 0.03	0.061 ± 0.04	0.56
Total insulin AUC 0-120	139.2 ± 43.48	131.0 ± 62.27	0.58	153.0 ± 51.71	164.8 ± 39.89	0.31
Inflammatory biomarkers						
IL-1b ($pg \cdot mL^{-1}$)	11.97 ± 1.24	12.36 ± 2.03	0.54	12.30 ± 1.97	12.20 ± 2.27	1
IL-6 ($pg \cdot mL^{-1}$)	112.00 ± 43.16	98.43 ± 47.49	0.29	85.90 ± 29.07	104.70 ± 27.62	**0.03***
IL-8 ($pg \cdot mL^{-1}$)	46.77 ± 12.66	49.02 ± 28.29	0.21	35.80 ± 28.42	55.00 ± 47.61	0.31
YKL-40 ($ng \cdot mL^{-1}$)	105.50 ± 70.40	146.80 ± 86.06	**0.05***	147.10 ± 103.30	148.70 ± 67.64	1
CRP-hs ($mg \cdot L^{-1}$)	5.53 ± 5.37	2.1 ± 1.37	0.43	7.28 ± 7	6.57 ± 7	0.81

Data are presented as mean ± SD.
P values were determined by paired *t*-test nonparametric.
Values in bold represent significant *P* values.
YKL-40, chitinase.
*Statistically significant, $P < 0.05$.

Stable values were observed in the CPET values, % FEV_1, % forced vital capacity (see Table, Supplemental Digital Content 2, Pulmonary and QoL characteristics, http://links.lww.com/MSS/A763) anthropometric data, energy expenditure, total daily steps (see Table, Supplemental Digital Content 1, Anthropometric and physical activity characteristics, http://links.lww.com/MSS/A762), or QoL (see Table, Supplemental Digital Content 2, Pulmonary and QoL characteristics, http://links.lww.com/MSS/A763) for 12 wk.

DISCUSSION

This is the first study, to our knowledge, that evaluates the effect of exercise on glucose profile in adult subjects with CF and abnormal glucose tolerance (INDET, IGT, or CFRD). We observe that 12 wk of a CEP in adults with CF and abnormal glucose tolerance can significantly improve glucose excursion after an OGTT. We also showed that the CEP increased their muscular strength.

We observe in the patients with CF that there was a significant decrease in the plasma glucose at 1 and 2 h during the OGTT without significant changes in plasma insulin levels in the CEP group. The magnitude of glucose tolerance improvement observed is comparable with the one observed (-1.5 $mmol \cdot L^{-1}$) in patients with T2D (31). As observed in patients with T2D (31), this improvement is mainly related to the positive effect of exercise on insulin sensitivity. Using indices derived from insulin and glucose measurements during OGTT, we observe an improvement of insulin sensitivity without effect on insulin secretion after the CEP (Table 2 and Fig. 1). Although the importance of reduced insulin sensitivity in CF is debated (9,21), a parallel between insulin sensitivity and glucose intolerance has been reported in patients with CF (2,8,9). In patients with T2D, some studies also reported a decrease in insulin secretion during the OGTT after 4 and 16 wk of exercise training (31). This decrease in insulin secretion is explained by the decrease needs in insulin as insulin sensitivity increase (31). We did not observe a significant change in insulin secretions in the present study in the exercise group. The absence of the adaptation of insulin secretion during the OGTT in patients with CF after exercise training is probably related to the well-documented alteration of physiological mechanisms involved in insulin secretion in CF (9,21). Indeed, insulin secretion in patients with CF is already decrease compared with individual without CF (9) and probably could not be decreased any further. Thus, our data suggest that even in a context of significant insulin secretion defect in adults with CF, insulin sensitivity improvement related to a CEP is associated with significant glucose tolerance improvement (Table 2).

Higher plasma levels of inflammatory biomarkers and cytokine, such as IL-1β, IL-6, and IL-8, are associated with reduced insulin sensitivity and can be improved by exercise training (15,16,25). We thus measured a panel of biomarkers to explore their effect on the training program. However, we did not observe significant changes in cytokines or inflammatory markers in our CF population, except for the YKL-40 protein, which is increased in the serum of the exercise group. YKL-40 is a glycoprotein that is released by neutrophils and macrophages. Higher plasma levels of YKL-40 were identified in multiple inflammatory diseases such as asthma and chronic obstructive pulmonary disease (18). YKL-40 was also shown to correlate with pulmonary function, disease severity, and increase in the serum of dysglycemic patients with CF (3). Interestingly, it has already been suggested that through its inhibitory effects on tumor necrosis factor α action, YKL-40 can positively effect on muscle insulin sensitivity (12) and, consequently, could be an autoprotective factor of skeletal muscle tissues. Our results are in concordance with this observation, thus suggesting that YKL-40, similarly to IL-6, is a biomarker of subclinical inflammation but can also have some anti-inflammatory activity (12).

Our training program improved maximal strength, and such improvements have already been observed in other CF training protocols (24,28). Such improvement is likely due to the resistance-training component of our training program that involves exercise of the quadriceps. This muscle is known to be weaker in patients with CF and thus is more susceptible to rapid improvement after training (32). Interestingly, improvements of strength have a positive effect on insulin sensitivity as well as glucose tolerance (31). However, similarly to other short-term training studies,

we observed no improvement for maximal aerobic capacity or FEV_1 (27,28). As suggested by Moorcroft et al. (19), a longer period of training could be required to observe stabilization in FEV_1 after an exercise training program. Further, larger training protocols should also address the potential benefits of exercise on multiple other CF relevant parameters such as bone density and QoL (27).

The magnitude of the improvement observed (-2.34 mmol·L^{-1} for second hour OGTT value and -17.2% for total glucose AUC) could translate into clinically relevant benefits such as a delay in CFRD occurrence (13,23) or potential improvement in lung function. However, because of the limitations (short duration and limited number of patients) of the present physiological study, it is premature to assume that the inclusion of exercise program in the CF therapeutic arsenal is possible and will have a long-term effect on disease evolution. Such hypothesis will need to be tested in prospective randomized controlled trials where an intent to treat analysis would be used to include all the patients recruited. The design and the length of the study protocol probably explain the lack of improvement in some parameters we have measured such as CPET value, QoL, inflammation, or fat-free mass, which have been previously reported (27) to improve with exercise program.

CONCLUSION

A CEP significantly improves glycemic control in patients with CF and dysglycemia, suggesting a therapeutic potential for this nonpharmacological approach, which could also have a positive effect on other important aspects of CF and supports the clinical burden of illness. However, such promising results should be confirmed in longer and larger trials.

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