The Evidence Regarding Exercise Training in the Management of Cystic Fibrosis: A Systematic Review

Michael J. Shoemaker, PT, DPT, GCS; Heather Hurt, SPT, BS; Leah Arndt, SPT, BS
Grand Valley State University, Physical Therapy Program, Grand Rapids, Michigan

ABSTRACT

Purpose: To conduct a systematic review of the evidence regarding the efficacy of exercise training in the management of cystic fibrosis (CF).

Methods: Articles were found by searching PEDRO, MEDLINE, and CINAHL databases. Included articles involved exercise-related interventions for long-term adaptations (ie, not acute effects of exercise). Articles were excluded if the language was other than English or if other non-exercise interventions were used. Date of publication was not a factor for exclusion. Two independent reviewers evaluated the included articles using Sackett's levels of evidence and select scoring criteria.

Results: Twelve articles were eligible for inclusion. Interventions studied included various aspects of exercise training: anaerobic, aerobic, or resistance training. Study end-points included pulmonary function, aerobic capacity, strength, and health-related quality of life (HRQL).

Conclusions: Exercise training in individuals with CF is beneficial, with aerobic and resistance training having the greatest support in the literature for improved aerobic capacity and strength, respectively. Exercise training does not appear to have an effect of improving pulmonary function, but may have a preservation effect. Strong conclusions about improvement in HQRL from exercise training cannot be made. However, greater consistency in measuring this outcome is needed in future trials. There is a paucity of evidence regarding the role of exercise training in reducing hospitalization and health care utilization, and questions raised by this review should be considered in the design of future trials.

Key Words: cystic fibrosis, aerobic exercise, review

INTRODUCTION

Cystic fibrosis (CF) is an autosomal recessive disease of the exocrine glands that affects almost 30,000 people in the United States.[1] Though CF is progressive, the rate of progression varies.[2] When first described in 1938, CF had a median survival age of less than 1 year.[2] By 2006, however, the mean survival age had increased to 37 years.[3]

Address correspondence to:
Michael J. Shoemaker, PT, DPT, GCS
Assistant Professor, Grand Valley State University
301 Michigan NE, Grand Rapids, Michigan 49503
(shoemami@gvsu.edu)

Cystic fibrosis is a multisystem disease, primarily affecting the pulmonary system and pancreas. Pancreatic insufficiency prevents adequate absorption of fats and fat-soluble vitamins, resulting in decreased muscle mass and lean body mass (LBM) despite adequate caloric intake.[1] Pulmonary abnormalities include excess production of viscous mucus secretions which may obstruct airways, leading to subsequent chronic and recurrent infections.[2] The course of the disease is marked by periodic exacerbations, resulting in increased coughing, decreased weight, and declining pulmonary function.[2] Many patients with CF refrain from physical activity due to fatigue and shortness of breath, which is now believed to be due not only to poor pulmonary function, but to deficits in skeletal muscle aerobic and anaerobic capacity and muscle strength as well.[4,5] Additionally, it has been observed that physically fit patients with CF typically live longer than their less-fit peers.[6]

As a result of these observations, there has been a recent focus in the literature regarding the impact of exercise on health-related quality of life (HRQL), aerobic capacity, anaerobic capacity, muscle strength, and pulmonary function. However, the research varies in the types of exercise and outcome measures used, making it difficult to determine the specific impact of exercise or make comparisons among studies. Bradley and Moran[7] conducted a systematic review in 2002. This analysis, however, was too narrow in the studies reviewed, and many of their conclusions were based on 2 studies. Thus, they excluded evidence from many weaker studies which can support or question conclusions of randomized controlled trials (RCTs). This, in addition to the emergence of several more recent studies investigating the effect of exercise in individuals with CF, has prompted the need for another systematic review of this significant intervention strategy. Therefore, the purpose of this systematic review was to investigate the efficacy of exercise training in the management of CF.

METHODS

A search for English articles in Physiotherapy Evidence Database (PEDro), Index Medicus (MEDLINE), and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) databases was conducted using "cystic fibrosis" and the following key words: "exercise," "aerobic training," "exercise training," "exercise program," "resistance training," "strength training," and "anaerobic training." The search was not limited by date of publication.

Study Selection Criteria

For inclusion in the systematic review, studies had to meet the following criteria: (1) the intervention was exercise-related, and (2) the study endpoints were related to longer-term adaptations or outcomes (ie, not acute effects of exercise). Studies were excluded from the systematic review if the language was other than English, or if the intervention was used in combination with any other non-exercise interventions.

Review Criteria

The strength of evidence was evaluated using Sackett's levels of evidence as described by Sackett[8] (Table 1). The levels are ranked 1 through 5 and represent the amount of confidence that can be placed in the results, with 1 being the most and 5 the least. Articles were independently ranked by the authors (HH and LA). If differences existed, a consensus was reached after discussion between the authors.

Table 1. Levels of Evidence

Level 1a =	Systematic Review of Randomized Controlled Trials (RCTs)
Level 1b =	RCTs with Narrow Confidence Interval
Level 1c =	All or None Case Series
Level 2a =	Systematic Review Cohort Studies
Level 2b =	Cohort Study/Low Quality RCT
Level 2c =	Outcomes Research
Level 3a =	Systematic Review of Case-Controlled Studies
Level 3b =	Case-Controlled Study
Level 4 =	Case Series, Poor Cohort Case Controlled
Level 5 =	Expert Opinion

Methodological Quality of Reviewed Studies

The methodological quality and rigor of each article was evaluated using a 10-point scale adopted from Medlicott and Harris.[9] Some of the items from the original scale were adjusted. Item 7 was modified from "including blinding of the patient, treatment provider, and assessor" to simply "blinding of the assessor."[9] This was more feasible for exercise studies, as it would be difficult to blind patients or treatment providers to group assignment. Also, Medlicott and Harris originally described item 9 as long-term results of 6 months or greater. However, there are few studies that have followed subjects with CF receiving exercise intervention over this period of time, and there could be beneficial effects of exercise that would be evident earlier than 6 months. Thus, we modified this item to follow-up of at least 1 month. The final criteria used in this review are summarized in Table 2.

Table 2. Scoring Criteria for Methodological Rigor

1	randomization
2	inclusion and exclusion criteria were listed for the subjects
3	similarity of groups at baseline (if the study used 2 or more groups)
4	the treatment protocol was sufficiently described to be replicable
5	reliability of data obtained with the outcome measures was investigated
6	validity data obtained with the outcome measures was addressed
7	blinding of assessor
8	dropouts were reported
9	long-term (1 month or greater) results were assessed via follow-up
10	adherence to home programs was investigated (if included in the intervention)

The original scoring system described by Medlicott and Harris gave each article a score based on the number of "yes" answers given. The total, out of 10 points, was then used to rank each article in terms of methodological strength. "Strong" articles had a total of 8 or higher, "moderate" was 6 to 7, and "weak" was less than or equal to 5.[9] However, as items 3 and 10 were not always applicable to the studies in this systematic review, the total scores were not always out of 10 possible points. Therefore, each score was converted into a percentage and subsequently ranked. Articles considered "strong" had a total score of 80% or higher, "moderate" scores were between 60% and 79%, and "weak" articles were less than 59%.

RESULTS

Two hundred and sixty articles were found with the search strategy outlined previously. The majority of these studies did not examine exercise training in the management of CF. Furthermore, of the studies that did, many combined exercise with other interventions for CF, such as airway clearance techniques, pharmacological interventions, or multifactorial management programs. Table 3 outlines the results of the literature search. Ultimately, 12 articles were eligible for inclusion in this review. The interventions used in these studies included various aspects of exercise training. One study investigated anaerobic training,[10] 6 considered aerobic exercise only,[11-16] 2 compared aerobic and resistance training,[17,18] and 3

Table 3. Search Methods and Results

Databases:	PEDro, CINAHL, MEDLINE via First Search
Search Terms:	"cystic fibrosis" and: "exercise," "aerobic training," "exercise training," "exercise program," "resistance training," "strength training," "anaerobic training"
Number of Articles Found:	260
Number of Articles Meeting Inclusion Criteria:	12
Excluded Articles:	
Reason	Number of Articles
Other exercise training-related topics, such as perceptions and attitudes	5
Non-English language	10
Acute effects of exercise	25
Airway clearance	7
Ventilatory muscle training	5
Exercise combined with other Interventions such as airway clearance, supplemental oxygen, medications	20
Other: review articles, commentaries, Non-exercise related topics	76

Table 4. Results of 10-Point Criteria: Methodological Rigor

Author	Randomized	Inclusion/ Exclusion Criteria	Similarity of Groups at Baseline	Replicable	Reliable	Valid	Blinding	Dropouts	Long-Term Results	Adherence	Total Score	Score as percentage	Level of Evidence
Klijn et al[10]	Y	Y	Y	Y	N	Y	Y	Y	Y	N/A	8/9	88.89%	1b
de Jong et al[11]	N	Y	N/A	Y	N	Y	N	Y	Y	Y	6/9	66.67%	2b
Gulmans et al[12]	N	Y	N/A	Y	N	Y	N	Y	N	Y	5/9	55.55%	2b
Orenstein et al[12]	N	Y	Y	Y	N	Y	N	Y	N	N/A	5/9	55.55%	2b
Schneiderman-Walker et al[14]	Y	Y	Y	Y	N	Y	Y	Y	N	Y	8/10	80.00%	1b
Turchetta et al[15]	N	Y	N/A	Y	N	Y	N	Y	N	N/A	4/8	50.00%	2b
Zach et al[16]	N	Y	N/A	N	N	Y	N	Y	Y	N/A	4/8	50.00%	2b
Orenstein et al[17]	Y	Y	Y	Y	N	Y	Y	Y	N	Y	8/10	80.00%	1b
Selvadurai et al[18]	Y	Y	Y	Y	N	Y	N	Y	Y	N/A	7/9	77.78%	1b
Braggion et al[19]	N	Y	Y	Y	N	Y	N	Y	N	N/A	5/9	55.55%	2b
Moorcroft et al[20]	Y	Y	Y	N	N	Y	N	Y	N	Y	6/10	60.00%	1b
Strauss et al[21]	N	Y	N/A	Y	N	Y	N	Y	N	N/A	4/8	50.00%	2b

Table 5. Study Characteristics

Authors	Design, Level of Evidence, and Rigor	Subjects	Interventions	OUTCOMES			
				FEV_1 and FVC	Aerobic Capacity	Strength	HRQL
Klijn et al[10]	RCT Level 1b Medlicott and Harris rating 88.9%	N=23, mean age 13.6, range 9-18 FEV_1 75% (21) FVC 85% (14)	2x/week for 12 weeks 30-45 min. sessions of 20-30sec anaerobic activities	No Change	No significant change from baseline $VO_{2\,peak}$ of 41.2 ml/kg/min for exercise group, but control group had significant decline W_{max} ↑ from 3.34 to 3.6 W/kg Anaerobic parameters all improved	Not Measured	CFQ scores improved Positive Perception of training program was noted
de Jong et al[11]	Cohort study Level 2b Medlicott and Harris rating 66.8%	N=10, mean age (SD) 20 (6.5) FEV_1 59% (23) FVC 75% (15)	7x/week for 12 weeks 21 min. of cycle ergometry at 70% predicted HR_{max}	No Change	$VO_{2\,peak}$ ↑ from 31.4 to 36.5 ml/kg/min W_{max} ↑ from 126 to 146 W (2.23 to 2.54 W/kg)	Not Measured	Improved DAL, but no data presented
Gulmans et al[12]	Cohort study Level 2b Medlicott and Harris rating 55.6%	N=14, mean age 14.1, range 10.2-16.4 FEV_1 58% (16) FVC 73% (17)	5x/week for 6 months 20 min. cycle ergometry at 70-80% predicted HR_{max}	No Change	$VO_{2\,peak}$ ↑ from 39.9 to 40.9 ml/kg/min W_{max} ↑ from 2.97 to 2.99 W/kg	Knee extensor strength ↑ from 159 to 195 N	SPPC scores improved Negative perception of training program was noted
Orenstein et al[13]	Cohort study Level 2b Medlicott and Harris rating 55.6%	N=31, ages 10-30 (no mean reported) FEV_1 61% (15) FVC 82% (21)	3x/week for 12 weeks progressed to 30 min. of jogging/walking at 70-80% predicted HR_{max}, followed by recreational games	FEV_1 of the control group significantly declined Ventilatory muscle endurance (sustained hyperpnea) improved	$VO_{2\,peak}$ ↑ from 33.6 to 38.25 ml/kg/min W_{max} ↑ but mean values and change not reported	Not Measured	Not Measured
Schneiderman-Walker et al[14]	RCT Level 1b Medlicott and Harris rating 80.0%	N=72, mean age 13.4, range 7-19 FEV_1 89% (19) FVC 93% (16)	3x/week for 3 years At least 20 min of subject-selected aerobic exercise at 70-80% predicted HR_{max}	FEV_1 and FVC declined significantly greater in the control group	Baseline $VO_{2\,peak}$ was 40.6 ml/kg/min, with an annual decline of nearly 2 ml/kg/min per year (not different than the control) W_{max} decreased annually, similar to the control	Not Measured	Improvement was noted, but not quantifiably reportable in comparison to the control group Partial to full adherence
Turchetta et al[15]	Cohort Study Level 2b Medlicott and Harris rating 55.0%	N=10, mean age 16.7, range 15-22 FEV_1 72% (25) FVC 73% (21)	2x/week for 3 months treadmill walking or running at 60% of peak HR, progressing 10% each month	No Change	$VO_{2\,peak}$ ↑ from 29.05 to 37.38 ml/kg/min	Not Measured	Not Measured
Zach et al[16]	Cohort Study Level 2b Medlicott and Harris rating 55%	N=10, mean age 10.5, range 2.5 – 16 FEV_1 71% (22) FVC 88% (15)	7x/week for 17 days, with 2 month post-discharge follow-up	No change was retained at 2 month follow-up	Not Measured	Not Measured	Not Measured

Orenstein et al[17]	RCT Level 1b Medlicott and Harris rating 80.0%	N=67, mean age 11.5, range 8-18 FEV_1 91.5% (17.92) FVC not reported	3x/week for 12 months progressed to 30 min. of stair stepper at 70% predicted HR_{max} or upper body resistance training exercise counseling	No change in FEV1 (effect on FVC not reported)	$VO_{2\ peak}$ was sustained in the aerobic exercise group (34.6 to 33.69 ml/kg/min); resistance training group declined in $VO_{2\ peak}$ (32.54 to 30.91 ml/kg/min) W_{max} ↑ in both groups; aerobic exercise 4.59 to 4.68 W/kg; resistance group 4.56 to 4.64 W/kg	Upper body strength improved more in the resistance training group, and lower body strength improved the most in the aerobic exercise group.	No Change in the QWB Scale for either group Larger drop-out rate in the aerobic exercise group
Selvadurai et al[18]	RCT Level 1a Medlicott and Harris rating 77.8%	N=66, mean age 13.2, range 8-16 FEV_1 57% (18) FVC 71% (17)	5x/week for 18 days, with 1 month post-discharge follow-up 30 min of treadmill or cycle ergometer for 30 min at 70% of peak HR or upper and lower body resistance training	Greatest improvement in FEV_1 in resistance training, followed by the aerobic exercise group	$VO_{2\ peak}$ ↑ from 33.8 to 41.3 ml/kg/min in the aerobic exercise group, compared to insignificant improvements of approximately 2.2 to 2.6 ml/kg/min in the resistance training and control groups	Knee extensor strength improved in the resistance training group (from 155Nm to 170Nm) compared to no change in the aerobic group and a decline of 4 Nm in the control group	QWB scale scores improved in the aerobic training group
Braggion et al[19]	Cohort study Level 2b, Medlicott and Harris rating 55.6%	N=10, mean age 12.5, range 11.1-15.3 FEV_1 77% (23) FVC 88% (18)	3x/week for 8 weeks 10-15 min. of stretching and flexibility exercise 10 min. of jogging and circuit-training exercises, initially, then progressed	No Change	$VO_{2\ peak}$ no change W_{max} ↑ from 4 to 4.2 W/kg	Not Measured	Not Measured
Moorcroft et al[20]	RCT Level 1b Medlicott and Harris rating 60.0%	N=51, mean age 23.5 (6.4) Approximate: FEV_1 57% FVC 75%	3x/wk for 12 months 20 minutes each of both aerobic exercise and upper body strengthening, individualized	Improved FVC of 0.46L vs decline of 1.46 L in control group	Reduced lactate concentration and HR during constant work rate cycle test	Not Measured	Positive Perception of training program was noted
Strauss et al[21]	Cohort Study Level 2b Medlicott and Harris rating 55.0%	N=9, mean age 24.7, range 16-39 FEV_1 42% (14) FVC 60% (16)	3x/week for 6 months upper and lower body resistance training	No Change	Not Measured	Number of muscle groups with normal strength doubled. Values for specific muscles not reported.	Positive perception of exercise protocol was noted.

CFQ = cystic fibrosis questionnaire, DAL = list of daily activities, FEV_1= forced expiratory volume in 1 second, expressed as percent predicted (standard deviation), FVC = forced vital capacity, expressed as percent predicted (standard deviation), HR = heart rate, HR= heart rate max, RCT = randomized control trial, SPPC = Self-Perception Profile for Children, VO_2max = mean maximal oxygen consumption, VO_2peak = mean peak oxygen consumption, W_{max}= mean maximum work capacity examined a combination of aerobic and resistance training.[19-21] Tables 4 and 5 present summaries of the methodological rigor and the characteristics of the included studies.

Levels of Evidence

Of the 12 studies reviewed, 5 were rated as level 1b evidence based on being RCTs with large sample sizes.[10,14,17,18,20] Five studies had a single-group pretest-posttest design with a control period involving no treatment.[11,12,15,16,21] Therefore, these studies were considered cohort studies and ranked as level 2b. In addition, 2 studies had control groups; however, there was no randomization or blinding involved in the studies.[13,19] Therefore, these were also considered cohort studies and ranked as level 2b.

Methodological Rigor

Study scores ranged from 50.00% to 88.89%. Three articles[10,14,17] were rated as "strong" ("yes" percentage of 80-100), 3[11,18,20] were judged "moderate" ("yes" percentage of 60-79), and 6[12,13,15,16,19,21] were determined "weak" ("yes" percentage of 59 or less).

Randomization

Subjects were randomly assigned in 5 studies.[10,14,17,18,20]

Subject inclusion and exclusion criteria

Inclusion and exclusion criteria varied among the studies, though all required a positive diagnosis of CF. Three studies specified disease severity for inclusion based on FEV_1.[10,12,14] Each study involved different ages, though only 7 provided specific age requirements.[10,11,14,15,17,18,21] One study investigated adults, but did not provide an exact age range.[20] Another study included any willing volunteers, regardless of age, from a CF center.[13] Also, 9 studies focused solely on children.[10,12,14-19,21] Selvadurai et al[18] studied children admitted for pulmonary exacerbation.

Six studies provided specific exclusion criteria. Gulmans et al[12] did not include children who had other concurrent diseases or CF-related symptoms such as pneumothorax or hemoptysis. Moorcroft et al[20] excluded adults who were participating in other studies, pregnant, on a transplant list, or diagnosed with cor pulmonale. Orenstein et al[17] excluded aerobically fit children, as determined by exercise test results. Schneiderman-Walker et al[14] excluded children if they were participating in other studies, had a record of noncompliance, or visited the clinic irregularly. Children were prevented from participating in the study conducted by Selvadurai et al[18] if they had a diagnosis of pulmonary hypertension or required daytime oxygen prior to their exacerbation and subsequent hospital admission. Strauss et al[21] excluded children deemed too ill to participate in the study.

Similarity of groups at baseline

The 7 studies that had a control group reported similarity of groups at baseline.[10,11,14,17-20]

Repeatability of the treatment protocol

Ten of the 12 studies had sufficient information to allow replication of the exercise programs.[10-15,17-19,21] The 2 remaining studies[16,20] lacked detailed parameters regarding interventions provided, thus making repeatability difficult.

Two of the studies considered repeatable did not include specific exercises performed by the subjects.[10,14] However, 1 study referenced a booklet provided to physiotherapists for use in conducting standardized exercise sessions;[10] the other gave specific exercise parameters, such as target heart rate and training times, thus meriting repeatability.[14]

Outcome measure reliability

None of the studies that were included reported any measures of intra- or inter-rater reliability. The only reference made to reliability of testing procedures used was made by Klijn and colleagues[10] with respect to the Wingate anaerobic test. However, no statement was made regarding investigators' skill in using the test.

Outcome measure validity

All studies used valid, standard cardiopulmonary measures to assess aerobic capacity, strength, and pulmonary function. Six studies used questionnaires to assess HRQL in their subjects.[10-12,14,15,18] Four studies provided validity data for their questionnaires.[10,11,17,18] Two lacked sufficient detail to determine validity.[12,14]

Blind assessment

Only 3 of the included studies reported blinding.[10,14,17] Klijn et al[10] blinded the primary researcher to the experimental condition. Orenstein et al[17] blinded both assessors and investigators. Schneiderman-Walker[14] blinded the pulmonary function technologists to group assignment.

Account for attrition

All studies accounted for attrition of subjects and included reasons for drop-out of participants.

Long-term follow-up

Long-term follow-up of 1 month or more was reported in 4 studies reviewed and ranged in duration from 1 month to 3 years.[10,11,16,18]

Adherence to home program

Only 5 studies involved home exercise programs, and all 5 reported to some extent on adherence.[11,12,14,17,20] de Jong et al[11] reported that all patients completed the exercise program. Participants in the study by Gulmans et al[12] were required to keep a 1 week diary of physical activity every 6 weeks. In addition, authors reported that the number of training sessions was noted. However, no information was provided regarding how well subjects adhered to the program. Moorcroft et al[20] required subjects to maintain an exercise diary. The investigators observed poor documentation of exercise in the diaries, leading researchers to question adherence. Orenstein et al[17] monitored adherence using portable heart rate monitors. Also, adherence was encouraged with financial incentives. However, no specific measure of adherence was provided. Schneiderman-Walker et al[14] promoted adherence by using exercise diaries and providing incentives. Mean scores for compliance were approximately 1.5 on a scale of 0 to 2, with 0 being poor adherence and 2 being full adherence.[14]

DISCUSSION

The purpose of this review was to determine the efficacy of exercise training in individuals with CF. The primary endpoints for the studies that were included were pulmonary function, aerobic capacity, strength, and HRQL. Interventions that were used included aerobic exercise,[11-14,16-20] anaerobic exercise,[10] and resistance training.[17,18,20,21] A previous review by Bradley and Moran[7] provided only tentative conclusions about the positive effect of aerobic or anaerobic exercise training on pulmonary function, aerobic capacity, and strength. However, the majority of these conclusions were based on only 2 studies. This review allows for more definite conclusions through the inclusion of additional and more recent evidence in addition to that presented by Bradley and Moran.[7]

The results of this review demonstrate that aerobic exercise training increases aerobic capacity. Five of 7 studies[11-13,15,18] demonstrated statistically significant improvements in peak oxygen consumption, and 6 of 7 studies[11-13,17,19,20] demonstrated statistically significant improvement in other measures of exercise capacity and performance such as peak work rate, as well as reduced lactate concentration and heart rate on a constant work rate test. Three of the 4 level 1b RCT's[17,18,20] investigating aerobic exercise demonstrated a positive effect on aerobic capacity. The fourth level 1b RCT[14] was in a population of those with predominantly mild disease (mean FEV_1 89% of predicted) and used a home-based program with slightly better than partial adherence.

Only 1 study examined the use of anaerobic training on aerobic capacity.[10] There was a prophylactic effect on peak oxygen consumption compared to the control group, and an increase in peak work rate. Two studies examined the effect of resistance training on aerobic capacity.[17,18] Both found no effect on peak oxygen consumption, and one demonstrated an increase only in peak work rate.[16] Thus, the use of anaerobic and resistance training to increase aerobic capacity is not well supported by the evidence.

Regarding the effect of exercise on pulmonary function (specifically FEV_1 and FVC), the preponderance of evidence suggests that improvement in lung function is not a likely result of exercise in this population. The evidence may suggest that there is a preservation effect, which could represent a clinically important outcome given that the annual rate of decline of FEV_1 percent predicted in CF has been documented to range from 1.12% in children to 2.34% in teenagers.[22] One level 1b RCT demonstrated no benefit at 3 month follow-up.[10] Another level 1b RCT showed a preservation benefit at 3 year follow-up.[14] Evidence of improvement was found in a level 1b RCT that showed improvement at 1 month follow-up for exacerbation-associated hospitalization[17] and another at 12 month follow-up.[20] Level 2b evidence overwhelmingly fails to demonstrate improvement in pulmonary function with follow-up periods between 2 and 12 months.[11,12,15,16,19,21] Thus, only prevention of decline through exercise and physical activity may be an expected result of exercise training. However, Boucher et al[23] found that activity level was not associated with FEV_1, even in individuals with moderate to severe lung disease (FEV_1 <75% of predicted). Selvadurai et al[24] also found no correlation between activity levels and lung function. More study is clearly needed with respect to the effect of exercise on this outcome.

Regarding the effect of exercise on strength, aerobic and resistance training both increase strength. Gulmans et al[12] (level 2b evidence) and Orenstein et al[17] (level 1b evidence) demonstrated significant improvement in lower extremity strength with aerobic training. Orenstein et al[17] and Selvadurai et al[18] (both Level 1b RCTs) demonstrated significantly improved strength with resistance training. No study allowed for any conclusions regarding whether aerobic or resistance training alone or in combination is optimal.

Regarding the effect of exercise training on HRQL, only 6 of the 12 included studies measured this important outcome.[10-12,14,17,18] Five of the 6 demonstrated improved HRQL. However, there was significant inconsistency in which instrument was used and how the results were reported. Instruments used included the list of daily activities (DAL),[11] Self-Perception Profile,[12] Cystic Fibrosis Questionnaire,[10] Quality of Well Being,[17,18] and a nonstandardized subject questionnaire.[14] All of these studies demonstrated an improvement in HRQL except a level 1b RCT by Orenstein et al[17] that included a 12-month intervention period. Thus, there may be a positive effect of exercise training on HRQL, but this conclusion is limited by the variety of measures used and negative evidence from a level 1b RCT. The lack of confidence in drawing conclusions about the effect of exercise is also shared by Abbott and Hart[25] in a critical review of HRQL across multiple types of interventions for individuals with CF, noting poor quality reporting across all studies they reviewed.

Notably absent from all but 1 of the studies included in this review was whether there was a beneficial effect of exercise training on hospitalizations in this population. Schneiderman-Walker et al[14] found no difference in number or duration of hospitalizations in their 3-year, home-based exercise intervention compared to the control group.

The inability to draw strong conclusions regarding the impact of exercise training on pulmonary function, HRQL, and hospitalization in individuals with CF raises several questions: What is the benefit of improved aerobic capacity and strength on these variables? How much does pulmonary function contribute to HRQL and hospitalization? Can interventions that do not improve pulmonary function still improve HRQL and hospitalization?

Observationally, several studies showed moderate correlations between peak oxygen consumption and FEV_1 with HRQL.[26-28] This would appear to be in agreement with the results of the present review where improvements in HRQL occurred with improvements in exercise capacity.[10-12,14,18]

Britto et al[29] did not find a strong association between lung function and HRQL, but those who declined to participate in their study had lower FEV_1 percent predicted indexes. However, they did observe strong negative correlations between HRQL and hospitalization. Yi et al[30] also found statistically significant declines in Physical Summary scores of the Child Health Questionnaire-Parent Form (PF-50) following hospitalization. The PF-50 measures HRQL in children ages 5-17. Only 1 study included in the present review measured hospitalization, and the authors found no effect of a 3-year, home-based exercise program.[14] Thus, it is not clear whether improvements in disease-specific measures such as aerobic capacity and strength from participation in exercise training will result in improvement in HRQL, hospitalization, and health care utilization, especially if pulmonary function is a strong mediating factor for these important outcomes.

It is well established in adults with COPD that rehabilitation interventions result in improvement in the disease specific measures of dyspnea, exercise tolerance, and HRQL, even without an improvement in pulmonary function.[31] There is emerging evidence that there is also a benefit on the reduction of health care utilization.[31] It is interesting to note that the strong relationship between exercise and HRQL is well-supported in the literature for adults with COPD, but not for individuals with CF. Perhaps the fact that CF, as a well-defined terminal condition that exerts its debilitating effects throughout an individual's development into adulthood, prevents improvements in impairments from translating into improved HRQL. Regarding hospitalization and health care utilization in individuals with CF, there is insufficient evidence to determine whether exercise training results in benefits similar to that found in adults with COPD.

Given that there have been no adverse effects of exercise training, there are improvements in aerobic capacity, and that there are likely benefits to HRQL, exercise training should continue to be considered an important part of an overall management program for individuals with CF.

Implications for future research

Future research is needed to provide greater clarity as to the effect of exercise training on pulmonary function and HRQL, and also the effect of exercise training on hospitalization, health care utilization, and mortality. Future research should also include more longitudinal studies that consistently and clearly report specific inclusion and exclusion criteria, exercise training protocols, and HRQL measures. This would allow for greater comparisons between studies and thus promote greater confidence in clinical application of the findings. Also, as more patients with CF are living longer, additional studies are needed to investigate the efficacy of interventions in adults.

CONCLUSION

The present systematic review on exercise training in individuals with CF incorporated evidence from considerably more studies than a previous review on the topic, and demonstrates that there is strong support for the use of aerobic and resistance training to improve aerobic capacity and strength, respectively. The effect of exercise training on pulmonary function is unclear, but appears to have a preservation effect. Also unclear is the effect of exercise training on HRQL due to inconsistency in measurement of this important outcome. Furthermore, no conclusions can be drawn regarding the role of exercise training in reducing hospitalization and health care utilization.

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