Influence of sex gap on muscle strength and functional mobility in patients with cystic fibrosis

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Abstract: The objectives of this study were to determine whether there were differences in handgrip strength and functional mobility between patients with cystic fibrosis (CF) and healthy controls with regard to sex and to ascertain whether these differences were related to lung function. Thirty-eight patients with CF (21 women) and 38 healthy controls aged 18–65 years were included. Muscle weakness and functional mobility were assessed through handgrip strength; walking speed; and time, velocity, and power derived from a single sit-to-stand (STS) test. Patients with CF showed differences for STS variables and walking speed but not for handgrip strength, compared with healthy controls. Considering sex differences, female patients showed differences for all variables analyzed while males with CF only exhibited differences for STS variables, compared with healthy controls. Females with CF showed moderate relationship between muscle weakness, functional mobility, and lung function ($|r| = 0.45–0.49$; $p \leq 0.05$) whereas no relationships were observed for males with CF. The influence of chronic infection with *Pseudomonas aeruginosa* and pancreatic insufficiency on muscle weakness and functional mobility was similar in both sexes. Differences in muscle strength and functional mobility were predominantly observed in females with CF. These results suggest an important effect of sex gap on muscle weakness and functional mobility in patients with CF.

Novelty

- The influence of sex gap on muscle weakness in CF has been shown.
- Muscle weakness was predominantly observed in females with CF.

Key words: cystic fibrosis, muscle weakness, power, sit-to-stand, handgrip, walking speed.

Résumé : Les objectifs de cette étude sont de déterminer s'il existe des différences de force de préhension manuelle et de mobilité fonctionnelle entre les patients aux prises avec la fibrose kystique (FK) et les témoins en bonne santé en tenant compte du sexe et de déterminer, le cas échéant, si ces différences sont liées à la fonction pulmonaire. Trente-huit patients aux prises avec FK (21 femmes) âgés de 18 à 65 ans et 38 témoins en bonne santé participent à cette étude. La faiblesse musculaire et la mobilité fonctionnelle sont évaluées à l'aide des tests suivants : la force de préhension manuelle, la vitesse de marche ainsi que la durée, la vitesse et la puissance dérivées d'un seul test assis-debout (« STS »). Comparativement au groupe de contrôle sain, les patients aux prises avec FK présentent des différences concernant les variables du STS et la vitesse de marche, mais pas pour la force de préhension manuelle. Compte tenu des différences entre les sexes, les patientes FK présentent des différences concernant toutes les variables analysées tandis que les hommes aux prises avec FK ne présentent, comparativement au groupe de contrôle sain, que des différences concernant les variables STS. Les femmes aux prises avec FK présentent une relation modérée entre la faiblesse musculaire, la mobilité fonctionnelle et la fonction pulmonaire ($|r| = 0,45–0,49$; $p \leq 0,05$) alors qu'aucune relation n'est observée chez les hommes aux prises avec FK. L'influence d'une infection chronique à *Pseudomonas aeruginosa* et d'une insuffisance pancréatique sur la faiblesse musculaire et la mobilité fonctionnelle est similaire chez les deux sexes. Des différences de force musculaire et de mobilité fonctionnelle sont principalement observées chez les femmes aux prises avec FK. Ces résultats suggèrent un effet important de l'écart entre les sexes de la faiblesse musculaire et de la mobilité fonctionnelle chez les patients aux prises avec FK. [Traduit par la Rédaction]

Les nouveautés

- L'influence de l'écart lié au sexe concernant la faiblesse musculaire dans la FK est démontrée.
- La faiblesse musculaire est principalement observée chez les femmes aux prises avec FK.

Mots-clés : fibrose kystique, faiblesse musculaire, puissance, test assis-debout, préhension manuelle, vitesse de marche.

Introduction

Cystic fibrosis (CF) is an autosomal recessive genetic disease caused by mutations of the CF transmembrane conductance regulator protein. The defect of this protein leads to pancreatic insufficiency (PI), chronic airway infection usually with *Pseudomonas aeruginosa* (CIP), and vigorous airway inflammation affecting progressively lung function (Kerem et al. 1992; Elborn et al. 1993; McKone et al. 2006). Although the prognostic of CF has continued

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to improve over the last decades, there is still a disadvantage in morbidity and mortality for females with CF (Kerem et al. 1992; Konstan et al. 2012), named the "CF sex gap".

Several factors have been proposed to this gap such as sex hormones estrogens leading to an earlier and higher rate of infections with *P. aeruginosa*, which generate a chronic inflammatory profile, altering respiratory transepithelial ion and fluid transport (Sweezey and Ratjen 2014). These factors aggravate the airways and cause tissue damage in patients with CF, increasing the prevalence of respiratory complications in females with CF.

While the focus of sex gap has been placed on the respiratory system, little is known about its influence on peripheral muscle strength. Elevated levels of proinflammatory cytokines, such as tumor necrosis factor alpha (TNF-α), have been associated with higher energy expenditure at rest, lower muscle mass, and strength deficits in females with CF, which could be considered a potential factor for chronic cachexia and muscle weakness (Elborn et al. 1993; Dufresne et al. 2009). However, the vast majority of studies analyzing muscle weakness between patients with CF and healthy controls have not conducted a separate sex-analysis (Elborn et al. 1993; Elkin et al. 2000; Pinet et al. 2003; Dufresne et al. 2009; Arikan et al. 2015) or have analyzed only a sex group (Selvadurai et al. 2003), making it difficult to identify sex differences. Another set of studies analyzing differences between males and females with CF have been designed without the inclusion of a healthy control group (Orenstein and Nixon 1991; Savi et al. 2015). While the results showed differences in favor of male patients, these studies move away from the purpose of analyzing the "CF sex gap", since these findings cannot be exclusively attributed to disease.

Since it is well established that this gap leads to a chronic inflammatory profile in females with CF, which impacts negatively on lung function (Sweezey and Ratjen 2014) and could influence muscle weakness (Elborn et al. 1993; Dufresne et al. 2009), one could expect relationships between lung function and muscle strength or functional mobility in these patients.

Therefore, the aims of this study were to (*i*) determine whether there were differences in muscle weakness and functional mobility determined from handgrip strength, self-selected walking speed, and sit-to-stand (STS) test between patients with CF and healthy controls with regard to sex; and (*ii*) ascertain whether these differences (if any) were related to lung function in patients with CF.

Materials and methods

Study design

An observational cross-sectional study design was conducted to compare muscle strength and functional mobility between patients with CF and healthy matched controls with regards to sex (clinicaltrials.gov no.: NCT03524859).

Study population

Study participants comprised adults diagnosed with CF and and healthy subjects matched for age (18–65 years), body mass index (24.2 (5.1) kg/m^2), and sex were enrolled in this study. Patients with CF were recruited from a specialized CF institution, the Cystic Fibrosis Association of Murcia, Murcia, Spain.

Patients had a stable clinical state, were not receiving long-term oxygen therapy or corticotherapy, and had normal-to-moderate lung disease (Schluchter et al. 2006). Patients treated with pancreatic enzymes were classified as PI. CIP was considered if there were 3 or more positive cultures for *P. aeruginosa* within a 6-month period, with an interval of at least 1 month between them or more than 50% of positive cultures within 12 months (Lee et al. 2003). Healthy subjects were recruited from the CF institution's staff and visitors to constitute a control group. Both groups had performed light to moderate physical activity representing an activity score of 3–4 according to the Grimby classification (Grimby 1988). This classification is based on a scale from 1 to 6 points, with higher scores indicating higher levels of physical activity.

This study was approved by the Ethical Committee of Catholic University of Murcia and all procedures conformed to the *Declaration of Helsinki*. All patients provided written informed consent.

Procedures and data analysis

Subjects attended the laboratory on 2 separate occasions, once for familiarization with the procedures and a week later for the experimental session. The experimental session involved the measurement of the STS test, handgrip strength, self-selected walking speed, and lung function.

The STS test was performed with subjects seated on a chair with their arms crossed over their chest and the hip, with knee and ankle joints positioned at approximately 90°. The instruction given to the subjects was to stand up as fast as possible. To minimize variability, participants performed 3 STS repetitions separated by 30 s of rest. The average total of the STS test for each participant was selected for futher analysis (individual coefficient of variation of 3 repetitions ranged between 0% to 23%). Each STS repetition was recorded on video at 240 frames-per-second using the iPhone app Sit-to-Stand (Sit-to-Stand App, version 1.0.8) installed on an iPhone 7 running iOS 11.4.1 (Apple Inc., USA). The iPhone was positioned on a 0.7-m high tripod placed 3 m from the chair on the right side of the subject as previously described (Ruiz-Cárdenas et al. 2018). Video analysis was undertaken by M.M.M.-G. following the app instructions (see Ruiz-Cárdenas et al. 2018 for more details). Then, the automatic app data response provides STS time, velocity, and power, which is reliable as a force plate (intra-class correlation coefficient >0.86) (Ruiz-Cárdenas et al. 2018). The app uses the following equation to calculate muscle power: $Y = 2.773 - 6.228 \times t + 18.224 \times d$, where t is the time of the rising phase, and d is the distance from sitting to upright position.

Handgrip testing was assessed using a digital hand dynamometer (Baseline Evaluation Instruments; Fabrication Enterprises Inc. White Plains, N.Y., USA). Each subject performed the trials in standing position with their upper arms at their side and the forearm into neutral. They were instructed to squeeze the device as hard as possible and standard verbal encouragement was given during each trial. The test was executed twice on both hands with 30 s of rest between trials and the greater of 2 trials from each hand were used and added together to give overall handgrip strength.

Self-selected walking speed was collected using a 4-m walking test. Subjects were instructed to walk at their normal comfortable pace over a distance of 8 m. Two meters were provided prior to and following the timed portion (4 m) to allow for acceleration and deceleration phases to occur outside the timed region and ensure that steady-state self-selected walking speed was captured for analyses. The test was completed 2 times to improve accuracy and the fastest was selected for further analysis. The 4-m walking test has shown excellent inter-observer reliability (intraclass correlation coefficient ≥0.91) (Kon et al. 2013; Bisca et al. 2018) and strong correlations (r = 0.77–0.78) with exercise capacity in patients with chronic obstructive pulmonary disease, as measured by either the 6-min walk test (DePew et al. 2013; Karpman et al. 2014) or the incremental shuttle walk test (Kon et al. 2013).

Pulmonary function test was performed in the sitting position with a spirometer (Sensormedics 2000; Sensormedics, Yorba Linda, Calif., USA) following the American Thoracic Society/European Respiratory Society recommendations (Miller et al. 2005). The best of 3 technically acceptable maneuvers was selected for analysis. The primary parameters of assessment were forced expiratory volume in 1 s (FEV1) and forced vital capacity (FVC). Values are expressed as percent of predicted values.

Table 1. Sample characteristics (n = 76).

	CF (n = 38)		Control (n = 38)	
	Male	Female	Male	Female
Sex, n (%)	17 (45)	21 (55)	17 (45)	21 (55)
Age, y	33.3 (13.8)	31.5 (11)	32.2 (12.4)	32.4 (10.2)
BMI, kg/m²	26.3 (6.8)	23.6 (3.8)	23.9 (4.2)	23.4 (5.1)
FEV1, % predicted	89.5 (23.8)	90.7 (23)	na	na
FVC, % predicted	98.9 (14.7)	101.7 (17.7)	na	na
PI, n (%)	11 (65%)	10 (48)	0 (0)	0 (0)
CIP, n (%)	9 (53)	9 (43)	0 (0)	0 (0)

Note: Data are given as means (SD) unless otherwise indicated. BMI, body mass index; CF, cystic fibrosis; CIP, chronic infection with *Pseudomonas aeruginosa*; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; na, not assessed; PI, Pancreatic insufficiency.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics 19.0 (IBM Corp., Armonk, N.Y., USA). Values are given in the text as mean and standard deviation or range of the mean with 95% confidence intervals (CIs). Data were normally distributed, as confirmed by the Shapiro–Wilks test. Homoscedasticity was confirmed by Levene's test. The level of statistical significance was set at $p \leq 0.05$.

The analysis of variance (ANOVA) was selected to determine differences in handgrip strength, self-selected walking speed, STS time, velocity, and power between patients with CF and healthy matched controls. A subgroup analysis of covariance (ANCOVA) was performed to evaluate the influence of sex gap on muscle weakness and functional mobility. Additionally, PI and CIP were used as covariables (confounders) into the model. The type I error was adjusted using Bonferroni correction for multiple comparisons. The results were interpreted using the 95% CI and the effect sizes were calculated as partial eta squared, which was interpreted as small (0.01–0.06), medium (0.06–0.14), or large (>0.14).

To evaluate the relationship between the muscle strength, functional mobility, and lung function, the Pearson's correlation coefficient was calculated.

Results

Subject characteristics

A total of 41 patients with CF were recruited in the present study. However, 3 of the patients with CF were excluded with severe lung disease (FEV1predicted ≤ 35%). Therefore, a total of 38 patients (17 females) with normal-to-moderate lung disease and 38 healthy matched controls (17 females) were analyzed (Table 1). A total of 21 (55%) patients had PI while 18 (47%) patients had CIP. Descriptive data for strength and functional mobility variables are given in Table 2.

Primary objective

Patients with CF showed a decline in functional mobility compared with healthy matched controls, but no differences were found for grip strength measurements (Table 3). However, considering sex differences, female patients showed slower STS time, velocity, power, and walking speed (all $p < 0.01$) and weaker grip strength (–11 kg; 95% CI: –19.2 to –4.3; $p = 0.002$) compared with female controls. Additionally, while male patients showed differences in STS variables (all $p \leq 0.001$), no differences were found for grip strength and walking speed compared with male controls. Furthermore, greater effect sizes were observed for all variables analyzed in female patients compared with male patients (Fig. 1).

Taking into account the influence of confounders (i.e., PI and CIP), the results indicated slightly lower differences between groups for all variables analyzed except for walking speed. The influence of both conditions was similar between males and females with CF (Table 3).

Secondary objective

Female patients showed significant relationships between muscle strength, functional mobility, and lung function variables whereas no relationships were found for male patients. Muscle strength determined by handgrip strength was positively associated to FVC ($r = 0.487$; $p = 0.02$) in females with CF. Additionally, moderate relationships were found between FEV1 and functional mobility derived from the STS test ($|r| = 0.43–0.45$; $p \leq 0.05$) whereas walking test showed no association with lung function variables (Table 4).

Discussion

The aims of this study were to (*i*) determine whether there were differences in muscle weakness and functional mobility determined from handgrip strength, self-selected walking speed, and STS test between patients with CF and healthy matched controls with regard to sex; and (*ii*) ascertain whether these differences were related to lung function in patients with CF.

Our results showed differences between patients with CF and healthy controls for STS variables and self-selected walking speed but not for handgrip strength when uncategorized analysis by sex was performed. However, considering sex analysis, female patients showed differences for all variables analyzed while males with CF only exhibited differences for STS variables, compared with healthy controls. Furthermore, greater differences between patients with CF and healthy controls were observed in female patients (Fig. 1), suggesting an important effect of sex gap in muscle strength and functional mobility.

Several studies have reported that muscle weakness in patients with CF ranged between 65% and 90% compared with healthy controls (depending on the muscle analyzed) with greater differences in lower limbs than upper limbs muscles (Elkin et al. 2000; Sahlberg et al. 2008). However, the vast majority of studies analyzing muscle weakness in patients with CF have performed uncategorized analyses by sex (Elborn et al. 1993; Elkin et al. 2000; Pinet et al. 2003; Dufresne et al. 2009; Arikan et al. 2015), which could not be suitable. If a sex-mixed analysis is performed, muscle abnormalities could be underestimated and even not detected, leading to wrong conclusions and incorrect clinical decisions.

An uncategorized analysis by sex proposed by Arikan et al. (2015) reported no differences in maximal handgrip strength in patients with CF, compared with healthy controls; whereas, similar to our study, Sahlberg et al. (2005, 2008) have twice reported differences in handgrip strength for female but not for male patients, compared with healthy controls. These results highlight our aforementioned suggestion that uncategorized analysis by sex could not be sensitive enough to detect differences in maximal handgrip strength between patients with CF and healthy subjects, possibly because the muscles of the upper limbs could be less affected than the lower limbs in these patients (Gruet et al. 2017).

Females with CF suffer more respiratory complications with an earlier and higher rate of infection of *P. aeruginosa*, leading to a chronic inflammatory profile with elevated levels of cytokines (Sweezey and Ratjen 2014). These factors cause damage to airways tissue, increasing the prevalence of respiratory complications in females with CF and have been associated to higher energy expenditure at rest, lower muscle mass, and strength deficits in patients with CF (Elborn et al. 1993; Dufresne et al. 2009). In our study, although similar characteristics were reported between males and females with CF with regards to FEV1 and FVC variables, females with CF showed moderate relationships between lung function, muscle weakness, and functional mobility but no relationships were observed for males with CF. These results suggest that muscle weakness and impairments in functional mobility could occur earlier in female patients because of a chronic inflammatory profile, which could lead to functional deficits during

Table 2. Muscle strength and functional mobility.

	STS time (s)	STS velocity (m/s)	STS power (W/kg)	Grip strength (kg)	Walking (s)
Total sample (n = 76)					
CF	0.564 (0.104)	0.713 (0.135)	6.26 (0.82)	64.4 (22.5)	2.9 (0.42)
Healthy	0.451 (0.062)	0.893 (0.116)	7.22 (0.65)	72.4 (19.2)	2.7 (0.33)
Male (n = 34)					
CF	0.552 (0.090)	0.745 (0.100)	6.54 (0.58)	85.6 (15.1)	2.8 (0.48)
Healthy	0.452 (0.053)	0.924 (0.123)	7.43 (0.65)	88.8 (15.5)	2.7 (0.32)
Female (n = 42)					
CF	0.574 (0.115)	0.687 (0.156)	6.04 (0.93)	47.3 (8.49)	3.0 (0.37)
Healthy	0.457 (0.069)	0.867 (0.106)	7.04 (0.61)	59.1 (8.76)	2.6 (0.34)

Note: Data are given as means (SD). CF, cystic fibrosis; STS, sit-to-stand.

Table 3. Between groups comparisons.

	STS time (s)	STS velocity (m/s)	STS power (W/kg)	Grip strength (kg)	Walking (s)
Total sample (n = 76)					
CF vs control	0.110 (0.070 to 0.149) $p \leq 0.0001$*	−0.18 (−0.237 to −0.122) $p \leq 0.0001$*	−0.95 (−1.29 to −0.61) $p \leq 0.0001$*	−7.9 (−17.5 to 1.6) $p = 0.105$	0.269 (0.093 to 0.445) $p = 0.003$*
Male (n = 34)					
CF vs controls	0.100 (0.041 to 0.160) $p = 0.001$*	−0.179 (−0.264 to −0.094) $p \leq 0.0001$*	−0.84 (−1.38 to −0.40) $p = 0.001$*	−3.2 (−11.4 to 5.0) $p = 0.445$	0.155 (−0.108 to 0.42) $p = 0.244$
Female (n = 42)					
CF vs controls	0.117 (0.064 to 0.170) $p \leq 0.0001$*	−0.180 (−0.272 to −0.103) $p \leq 0.0001$*	−1.00 (−1.45 to −0.56) $p \leq 0.0001$*	−11.7 (−19.2 to −4.3) $p = 0.002$*	0.361 (0.125 to 0.59) $p = 0.003$*
Male (n = 34)					
CF vs controls adjusted by PI and CIP	0.076 (0.004 to 0.148) $p = 0.036$*	−0.150 (−0.225 to −0.045) $p = 0.006$*	−0.69 (−1.29 to −0.09) $p = 0.026$*	−1.9 (−12.1 to 8.3) $p = 0.713$	0.32 (0.003 to 0.635) $p = 0.048$*
Female (n = 42)					
CF vs controls adjusted by PI and CIP	0.100 (0.038 to 0.162) $p = 0.002$*	−0.159 (−0.249 to −0.069) $p = 0.001$*	−0.85 (−1.37 to −0.34) $p = 0.002$*	−10.8 (−19.5 to −2) $p = 0.017$*	0.492 (0.221 to 0.763) $p = 0.001$*

Note: Data are given as means differences (95% confidence interval) and p value. All comparisons were adjusted by Bonferroni correction. CF, cystic fibrosis; CIP, chronic infection with *Pseudomonas aeruginosa*; PI, pancreatic insufficiency; STS, sit-to-stand.

*Significant differences at an α level of 0.05.

Fig. 1. Effect sizes for between-group comparisons with regard to sex. Muscle weakness is interpreted using partial eta squared and 90% confidence interval (CI). Filled symbols represent female sex whereas empty symbols represent male sex. Grey areas are interpreted as small, medium, or large effect sizes, respectively, with more lightness representing greater effect. Note that this graphical representation did not consider confounder variables. CF, cystic fibrosis; STS, sit-to-stand.

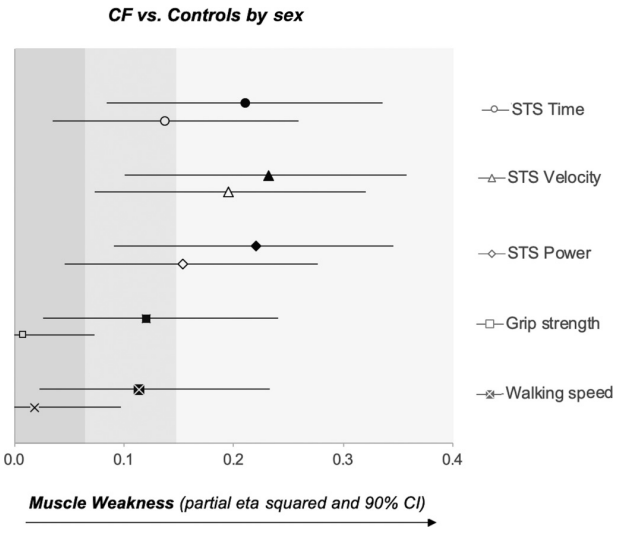

Table 4. Relationship between muscle strength, functional mobility, and lung function in patients with cystic fibrosis (n = 38).

	Males (n = 17)		Females (n = 21)	
	Correlation coefficient	p	Correlation coefficient	p
FEV1, % predicted				
STS time (s)	−0.023	0.93	−0.432	0.05*
STS velocity (m/s)	−0.086	0.74	0.441	0.04*
STS power (W/kg)	0.104	0.7	0.446	0.04*
Grip strength (kg)	0.076	0.77	0.304	0.18
Walking (s)	−0.10	0.70	0.08	0.71
FVC, % predicted				
STS time (s)	−0.060	0.82	−0.276	0.23
STS velocity (m/s)	−0.109	0.68	0.293	0.2
STS power (W/kg)	0.124	0.63	0.371	0.98
Grip strength (kg)	0.092	0.72	0.487	0.02*
Walking (s)	−0.24	0.35	0.05	0.84

Note: FEV1, forced expiratory volume in one second; FVC, forced vital capacity; STS, sit-to-stand.

*Significant correlation at an α level of 0.05.

activities of daily living. Unfortunately, this study did not measure the levels of cytokines (e.g., TNF-α or interleukin-8) in our sample, and these relationships could be due to another confounding factor. Therefore, this suggestion should be interpreted with caution.

Underlying mechanisms of muscle weakness in patients with CF is challenging as several factors probably act together and their relative influence may vary between individuals (Gruet et al. 2017). Some proposed factors include physical inactivity, inflammatory profile, and metabolic abnormalities caused by the progression of CF disease being possibly more affected in female patients (Gruet et al. 2017). The results from our study are in line with these

findings; those patients with PI and CIP suffered greater differences in muscle strength and functional mobility. The influence of both conditions was similar in both sexes and accounted from 1% to 24% of muscle weakness, depending on the test analyzed, with greater influences in lower limbs. However, some authors have not reported influence of PI on muscle weakness in patients with CF (Sahlberg et al. 2005, 2008). Inconsistency between studies might arise from the selection of both variables as confounders into the statistical model, i.e., PI together with CIP, rather than taking into account PI alone and performing a subgroup analysis limiting statistical power.

Early detections of contributing factors of muscle weakness in patients with CF is crucial to elaborate specific and individualized interventions to improve peripheral muscle impairments, health-related quality of life, and mortality. Muscle power declines with aging at an earlier and faster rate compared with muscle mass and strength (Reid et al. 2014) and recently this is being studied in patients with CF (Rietschel et al. 2008; Radtke et al. 2017; Sheppard et al. 2019). Although time to complete the STS test is the primary measure of function, STS velocity and power were more sensitive to detect changes related to disease progression compared with STS time, handgrip strength, and self-selected walking speed in patients with CF. Rietschel et al. (2008) performed 3 months of whole-body vibration training in patients with CF and their results showed improvements in STS velocity and power by +0.1 m/s and +2.38 W/kg, respectively. These results suggest that a similar training program executed in our sample could overcome control values, highlighting the importance of exercise training in patients with CF.

Exercise training is the most effective intervention to address peripheral muscle weakness and should be strongly recommended in patients with CF. However, muscle adaptations to exercise training could be different in males with CF compared with females (Sahlberg et al. 2008; Gruber et al. 2011). Sahlberg et al. (2008) performed 2 different types of training (endurance and resistance training) in patients with CF according to patient preferences. Their results showed some improvements in muscle strength for males with CF after 3 months of training whereas no improvements were shown for any variable analyzed in females with CF regardless of the type of training. Since muscle weakness could occur earlier and faster in female patients, clinicians should keep in mind the sex gap in patients with CF in exercise interventions because specific therapeutic goals and training stimulus could vary depending on the sex of the patients. Further research should investigate training responses with regards to sex in patients with CF.

Despite a rigorous approach towards data collection and synthesis, this study is not without limitations. First, it was a cross-sectional study, and therefore longitudinal studies are warranted to determine the influence of sex gap on peripheral muscle strength and functional mobility in patients with CF. Second, the patients recruited in this study had preserved lung function, which is not common in this population. Even so, differences were shown between patients with CF and healthy controls, highlighting the importance of assessing peripheral muscle strength in patients with CF regardless of lung function. Third, reduced muscle mass is highly related to strength deficits in patients with CF (Elkin et al. 2000); however, it was not measured in our study. To perform between-group comparisons adequately, muscle power relative to body mass was used and controls subjects were matched for age, sex, nutritional status, and had similar levels of physical activity. Finally, questionnaires for monitoring physical activity levels are useful to describe the sample and generate discussion on physical activity patterns in cross-sectional studies; however, motion sensors (e.g., SenseWear and ActiGraph) are preferable for monitoring physical activity when it is used as a primary outcome in longitudinal studies (Bradley et al. 2015). Further longitudinal studies monitoring physical activity levels should consider analyzing the CF sex gap to elucidate the main responsible mechanism(s) of this gap. The studies could be designed performing a fatigue test, since fatigue is a major symptom of chronic respiratory disease (Gruet 2018).

In conclusion, differences in muscle strength and functional mobility were predominantly observed in females with CF. These results suggest an important effect of sex gap on muscle weakness and functional mobility in patients with CF that have preserved lung function.

Conflict of interest statement

The second author of the article is the creator of the app and may benefit financially from purchases of the app. Nevertheless, to guarantee the objectivity of the results, the first author performed data analysis from the app. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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