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Original Article

The relationship between lung function, exercise capacity, oxidant and antioxidant response in primary ciliary dyskinesia and cystic fibrosis

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ABSTRACT

Background. There is a need to identify the complex interplay between various physiological mechanisms in primary ciliary dyskinesia (PCD) and cystic fibrosis (CF). The study investigated the interaction between respiratory function, exercise capacity, muscle strength, and inflammatory and oxidant/antioxidant responses in patients with PCD and CF.

Methods. The study included 30 PCD patients, 30 CF patients, and 29 age and sex-matched healthy subjects. Exercise capacity was assessed using the modified shuttle walk test (MSWT). Handgrip strength (HGS) was used to evaluate general muscle strength. Oxidative stress-inflammatory parameters were also assessed. Pulmonary function test was performed by spirometry. Regarding the forced expiratory volume in 1 second (FEV_1) z-score, patients with PCD and CF were subdivided into normal, mild, and severe/moderate groups.

Results. Forced vital capacity (FVC) z-scores were lower in PCD and CF patients than controls. FEV_1, FEV_1/FVC, peak expiratory flow (PEF), and forced mid expiratory flow ($FEF_{25-75\%}$) z-scores were lower in PCD than in the other groups. HGS was lower in both mild PCD and normal CF patients relative to the controls. MSWT distance was lower in severe/moderate PCD patients than controls. Catalase (CAT), glutathione S-transferase (GST), glutathione peroxidase (GPx), and malondialdehyde (MDA) levels did not differ significantly among the study groups, but superoxide dismutase (SOD) level in severe/moderate PCD, and glutathione (GSH) level in normal CF were higher than in controls. Interleukin-6 (IL-6) level was higher in patients with normal PCD and CF compared to the controls. IL-1β level was higher in PCD compared to controls. Additionally, correlations among these parameters were also determined in some patient groups.

Conclusion. Homeostasis related to respiratory function, aerobic performance, muscle strength, inflammatory response, and oxidant/antioxidant balance were affected in PCD and CF. Evaluating these mechanisms together may contribute to elucidating the pathophysiology of these rare diseases.

Key words: aerobic performance, handgrip strength, primary ciliary dyskinesia, cystic fibrosis, oxidative stress-inflammatory parameters.

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Primary ciliary dyskinesia (PCD) (ORPHA: 244) is an autosomal inherited recessive disorder characterized by structural and functional defects of motile cilia.[1,2] Ciliary dysfunction disrupts mucociliary transport and results in recurrent infections occurring in the upper and lower respiratory tract.[3]

Cystic fibrosis (CF) (ORPHA: 586) is an inherited, multisystemic disease caused by a defect in the cystic fibrosis transmembrane conductance regulator (CFTR) protein. CFTR is mainly a chloride ion channel, but it also regulates other membrane channels and facilitates mucociliary clearance. Patients with CF cannot adequately clear this thickened mucus which causes chronic inflammation, airway damage, infections, and eventually respiratory failure.[4,5] Therefore, management of the respiratory tract is critical in patients with CF as well as in patients with PCD. Previous comparisons of PCD and CF have revealed that exercise capacity, which provides important information about global health, morbidity, and mortality, is consistently reduced in children with PCD and CF.[6–8] Limited information is available on the mechanisms of decreased exercise capacity in PCD and CF.

In the literature, the effect of the oxidant-antioxidant balance on the pathogenesis and progression of many diseases has been evaluated.[9–11] This balance and inflammation are vital for cell viability, proliferation, and function in PCD and CF.[12,13] Tucker et al.[14] stated that oxidative stress caused a decrease in respiratory function in patients with CF. In addition, there is a link between oxidative stress and exercise capacity in various patient groups.[15] We aimed to elucidate the relationship between respiratory function, exercise capacity, muscle strength, inflammatory response, and oxidant-antioxidant balance in patients with PCD and CF to comprehensively investigate the pathophysiological mechanisms underlying respiratory disease in these patients. We hypothesized that PCD and CF patients would exhibit poorer pulmonary function, exercise capacity, and muscle strength than healthy subjects, and this alteration is associated with an augmented inflammatory response and an imbalance in the oxidant-antioxidant equilibrium in these patients. Establishing these relationships would enable us to take adequate steps towards advancing the multifactorial nature of these diseases and facilitating the development of effective therapeutic interventions.

Methods

Study design and subjects

The study was conducted at Pediatric Pulmonology Department of Hacettepe University Hospital between March 2018 and February 2020. In addition, it was approved by Hacettepe University Noninterventional Clinical Research Ethics Committee with approval no: GO 18/194 on 13 February 2018.

This study included a total of 89 volunteers aged 6-18 years and was divided into three groups: PCD (n=30), CF (n=30), and healthy subjects (n=29). The sample size was calculated using sample size software (G*Power version 3.1.9.2, Germany) with parameters set at 90% power, $\alpha = 0.05$, $\beta = 0.1$. In addition, patients with PCD and CF were subdivided into normal, mild, and severe/moderate groups according to their the FEV_1 z-score. Patients, healthy subjects, and their parents signed an informed consent form. The control group consisted of 30 subjects, but one healthy subject was excluded due to withdrawing family consent to participate.

The diagnosis of PCD was made according to the recent guidelines,[16] and a combined approach of complementary methods was applied. The PCD group considered clinical and radiological findings, genotyping, nasal nitric oxide level, transmission electron microscopy, ciliary beat pattern, and frequency criteria.[17] The diagnosis of CF was established upon typical clinical findings, with at least two positive sweat chloride tests and/or two CF-causing *CFTR* mutations.[18] Exclusion criteria were being clinically unstable (respiratory, cardiovascular, neurological, etc.), taking systemic steroids, having a recent history

of pulmonary exacerbations (the previous 30 days), having a FEV_1 of ≤40%, and not being able to perform exercise tests for the PCD and CF patients. Patients who met the inclusion criteria during the study were recruited according to age and sex similarity. In addition, the control group included participants who had no systemic or acute illness, physical health problems and were matched for age and sex.

All patients' and healthy subjects' socio-demographic and clinical characteristics were recorded, and body mass index (BMI) was calculated. BMI-for-age z-scores were calculated using the World Health Organization (WHO) anthropometric calculator (AnthroPlus v.1.0.4) based on WHO Child Growth Standards and Growth Reference data. Physical examination, lung function test, and blood sample collection were performed in all patients with PCD, CF, and healthy subjects. Exocrine pancreatic insufficiency status, fat-soluble vitamin values, and usage of modulator therapy were also recorded. Additionally, pulse oxygen saturation (SpO_2) evaluated in room air was recorded when the participants were recruited into the study.

Spirometry

A spirometer (Vyntus™ SPIRO PC Spirometer, Mettawa, US) was used to perform the pulmonary function tests. The FEV_1, forced vital capacity (FVC), FEV_1/FVC, forced midexpiratory flow 25–75% ($FEF_{25–75}$%), and peak expiratory flow (PEF) were measured according to European Respiratory Society (ERS) standards.[16] Airflow limitation classification was based on the z-score of FEV_1 according to American Thoracic Society (ATS)/ERS recommendations (z-score >-1.645: Normal, between -1.645 and -2.5: Mild, between -2.51 and -4: Moderate, and <-4: Severe.[19] In this study, patients with PCD and CF were classified as normal, mild, moderate, and severe in terms of FEV_1 z-score and intra-group statistical comparisons were performed between those classified as normal, mild, and severe/moderate.

Standard microbiological assessment

The sputum samples were obtained when the patients were recruited into the study. Sputum samples were inoculated on BD Columbia agar with 5% sheep blood; at the same time, sputum samples were inoculated with BD Mac Conkey II agar BD chocolate agar. Sheep blood agar and chocolate agar were incubated at 37 °C with a 5% CO_2 incubator, but Mac Conkey agar at 37 °C incubator. The isolates were identified based on colony morphology, Gram staining, conventional methods, and matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI Biotyper C System [Bruker Daltonics, Germany]). Intracellular and pathogenic bacteria in sputum were evaluated.

Additionally, the bacterial colonization was considered chronic when more than 50% of the preceding 12 months were culture-positive.[20]

Physical activity

Physical activity level (PAL) was determined using the Bouchard Three-Day Physical Activity Record. Physical activities were recorded at 15 minute intervals for three days (two consecutive weekdays and one day for the weekend). A scale from 1 (sedentary activity) to 9 (intense manual work or high-intensity sports) was used to qualify energy expenditure as the approximate median energy cost in kcal/kg/15 min. The mean value from the three days was considered for the analysis.[21]

Aerobic performance

A modified shuttle walk test (MSWT) was used to evaluate exercise capacity. Both before and after the test, heart rate was measured using telemetry (Polar S 610i, Lake Success, New York, USA), blood pressure by using a manual sphygmomanometer (Erka Perfect Aneroid Sphygmomanometer, Germany), and SpO_2 by using a portable pulse oximeter (Finger Pulse Oximeter, Germany). In addition, dyspnea and general fatigue were evaluated in all groups.[22]

Handgrip strength

A baseline hand dynamometer (Baseline Standard Hydraulic Hand Dynamometer, 90 kg, Baseline, New York, USA) was used to determine the handgrip strength (HGS). The HGS was measured in a sitting position, with the elbow in 90 degrees of flexion, and the forearm and wrist in a neutral position. In order to reduce the effects of muscle fatigue, a one-minute break was given between measurements.[23] The hand dynamometer was squeezed with maximum force throughout the test and held for three seconds.[24] In addition, each muscle group was tested bilaterally and recorded in Newtons (N), with an average value of three reproducible attempts.

Oxidant-antioxidant and inflammatory parameters

Blood samples were drawn via forearm venous puncture and collected into heparinized vacutainer tubes, and samples were collected and kept in sterile containers. Plasma samples were obtained through 10 minutes of centrifugation at 2000 rpm. All plasma samples were aliquoted into 2 mL eppendorf tubes and stored at −80°C until analysis. In these samples, glutathione (GSH), catalase (CAT), superoxide dismutase (SOD), glutathione S-transferase (GST), and glutathione peroxidase (GPx) levels were investigated to evaluate antioxidant status. On the other hand, malondialdehyde (MDA) level as a lipid peroxidation marker was measured to assess oxidant status. In addition, interleukin (IL-1β, IL-6, IL-8) levels were detected in plasma through a sandwich enzyme immunoassay to determine leukocyte activation.

All experiments were carried out using an ELISA kit (Cloud-Clone Corp., USA), following the protocol provided by the manufacturer and absorbance was read at 450 nm using a microplate reader (SpectraMax® M5 Microplate Reader, Molecular Devices LLC, USA).

All experiments based on oxidant-antioxidant balance and inflammation parameters were carried out with technical duplicates.

Statistical analysis

Statistical analysis was conducted using IBM SPSS 23.0. (SPSS Inc., Chicago, USA). Numerical variables were summarized by mean±standard deviation or median [25-75th percentile] as appropriate. Categorical variables were shown as frequencies and percentages. The differences in numerical variables between independent groups were analyzed using the one-way ANOVA when variables were normally distributed and group variances were homogeneous. Welch ANOVA compared groups when variables were normally distributed, and group variances were heterogeneous. Posthoc comparisons were performed by Tukey HSD or Games Howell test, respectively. Kruskal Wallis test was used when the distribution of the variables was not normal. The Dunn test made pairwise comparisons. Mann Whitney U test was used to show differences between two independent groups in terms of continuous variables those not normally distributed. Relations between categorical variables were determined by using the chi-square test. The Spearman correlation coefficient (r) was used to determine the association between continuous variables. The values of $p<0.05$; $p<0.01$; $p<0.001$ were considered statistically significant.

Results

Demographic characteristics and clinical laboratory values for study groups are presented in Table I. The groups were similar in age and sex ($p>0.05$). Median FVC z-scores were lower in the PCD and CF patients than in the healthy subjects ($p<0.001$). In addition, median FEV_1, FEV_1/FVC, PEF , and $FEF_{25-75\%}$ z-scores were lower in the PCD patients compared to the other groups ($p<0.001$). In addition, *Haemophilus influenzae* was the predominant microorganism detected in 60% of the PCD patients, and 3.3% of patients exhibited chronic colonization by both *H. influenzae* and *Pseudomonas aeruginosa*. The results obtained from CF patients showed that methicillin-susceptible *Staphylococcus aureus*

Table I. Characteristics of PCD and CF patients and healthy subjects.

Characteristic	Healthy (n=29) (Mean ± SD)	PCD (n=30) (Mean ± SD)	CF (n=30) (Mean ± SD)	p value
Age (years)	13.8±3.2	13.6±3.5	13.4±3.4	0.920
Gender (F/M)	17/12	17/13	17/13	0.985
Weight (kg)	54.45±17.30	47.71±18.97	44.01±13.33	0.057
Height, z-score	0.14±0.96	-0.10±1.26	-0.55±1.21	0.073
BMI, z-score	0.15±2.05	-0.06±1.31	-0.36±1.05	0.425
O_2 saturation (%)	97±2	96.2±1.6	96.4±1.5	0.563
FVC, z-score	0.3±1.2[a]	-1.9±1.7[b]	-1.1±1.8[b]	<0.001*
FEV_1, z-score	1.1±1.0[a]	-2.4±1.7[b]	-0.8±2.1[c]	<0.001*
FEV_1/FVC, z-score	1.6±1.2[a]	-1.3±2.1[b]	0.4±1.7[c]	<0.001*
PEF, z-score	-0.02±1[a]	-1.8±1.3[b]	-0.7±1.1[a]	<0.001*
$FEF_{25-75\%}$, z-score	0.8±1.2[a]	-2.8±1.4[b]	-1.1±2[c]	<0.001*

Same parameters carrying different letters (a,b,c) are statistically different at *p<0.001.
BMI: body mass index, CF: cystic fibrosis, F/M: Female/Male, $FEF_{25-75\%}$: forced expiratory flow 25–75%, FEV_1: forced expiratory volume in one second, FVC: forced vital capacity, PCD: primary ciliary dyskinesia, PEF: peak expiratory flow, SpO_2: oxygen saturation, SD: standard deviation.

(MSSA), *P. aeruginosa*, and methicillin-resistant *S. aureus* (MRSA) were detected in 66.6%, 20%, and 6.6% of cases, respectively. Additionally, 6.6% of these patients displayed chronic colonization by both MSSA and *P. aeruginosa*. All patients had been diagnosed with exocrine pancreatic insufficiency and were prescribed pancreatic enzyme replacement therapy alongside vitamin supplements. Notably, none of the patients were undergoing modulator therapy during the study period. Among the CF patients, three exhibited vitamin A deficiency, two had vitamin E deficiency, and an additional two presented with vitamin D deficiency.

There was no significant difference among study groups in terms of PAL (p>0.05). Median MSWT distance was lower in severe/moderate PCD patients compared to healthy subjects (p=0.005, Table II). Median HGS level was lower in both mild PCD and normal CF patients than in healthy subjects (p=0.013, Table II and III).

According to the results of oxidant-antioxidant parameters, CAT, MDA, GPx, and GST levels did not differ between study groups (p>0.05). In addition, the SOD level was higher in the severe/moderate PCD patients than in the healthy subjects (p=0.037, Table II) while the GSH level was higher in normal CF compared to healthy subjects (p=0.027, Table III). Regarding inflammation parameters, IL-6 level was higher in patients with normal PCD and CF relative to healthy subjects (p=0.002, Table II; p=0.015, Table III, respectively). Additionally, IL-1β level was higher in PCD patients than in healthy subjects (p<0.001, Table II) while the IL-8 of PCD patients tended to be higher compared to healthy subjects (p=0.052, Table II).

In this study, the correlation coefficients were calculated for each study variable of PCD patients and their significant relationships are demonstrated in Table IV. Findings can be listed as follows: GSH significantly correlated with MDA (r =0.404, *p=0.027). GPx significantly correlated with CAT, IL-6, IL-8, IL-1β, and HGS levels (r=-0.376, *p=0.044; r=0.394, *p=0.034; r=0.387, *p=0.035; r=0.560, **p=0.002; r=-0.362, *p=0.049, respectively). IL-6 significantly correlated with IL-8 and IL-1β levels (r=0.430, *p=0.020; r=0.684, **p<0.001, respectively). In addition, there was a positive correlation between IL-8 and IL-1β levels (r=0.422, *p=0.023). PAL significantly correlated with HGS levels (r=0.392, *p=0.035).

Table II. Comparison of physical activity level, handgrip strength, aerobic performance, oxidant-antioxidant, and inflammatory parameters in healthy subjects and PCD patient groups based on FEV_1 z-score.

Study Parameters	Healthy Subjects (n=29)	Severe/Moderate PCD Patients (n=10)	Mild PCD Patients (n=9)	Normal PCD Patients (n=11)	p value
PAL	2.33 [2 – 2.61]	1.73 [1.53 – 2.46]	2.09 [1.58 – 2.27]	2.35 [1.88 – 2.63]	0.193
HGS (kg)	24 [16.51 – 29.07]^{a}	16.88 [10.62 – 25.26]^{ab}	13.5 [8.82 – 18.64]^{b}	24.75 [16.88 – 40.13]^{ab}	0.013
MSWT distance (m)	810 [680 - 990]^{a}	530 [425 - 700]^{b}	590 [495 - 785]^{ab}	700 [580 - 840]^{ab}	0.005
GSH (μg/mL)	2196.06 [390.89 – 7878.13]	8439.46 [101.3 – 17561.28]	7725.65 [3739.18 – 9850.45]	6322.46 [605.94 – 7871.02]	0.354
CAT (ng/mL)	0.23 [0.15 – 0.39]	0.26 [0.15 – 0.35]	0.51 [0.3 – 0.66]	0.24 [0.13 – 0.43]	0.096
SOD (pg/mL)	948.8 [774.67 – 1036.42]^{a}	1123.25 [1007.84 – 1359.74]^{b}	968.93 [847.11 – 1732.58]^{ab}	897.87 [845.08 – 1087.75]^{ab}	0.037
GPx (ng/mL)	3.33 [2.14 – 5.76]	3.88 [3.21 – 9.47]	3.83 [3.11 – 5.95]	4.91 [3.11 - 8]	0.500
MDA (ng/mL)	8599.44 [6660.51 – 10252.38]	9663.4 [7081.17 – 11144.64]	8110.34 [6898.31 – 12307.18]	9693.82 [8271.97 – 12593.26]	0.272
GST (ng/mL)	7.94 [3.41 – 14.15]	4.49 [2.55 – 7.58]	6.55 [4.12 – 13.58]	11.15 [4.54 – 61.57]	0.186
IL-6 (pg/mL)	39.89 [17.78 – 81.44]^{a}	160.39 [116.58 – 236.27]^{ab}	180.92 [146.37 – 226.63]^{ab}	171.51 [136.99 – 413.28]^{b}	0.002
IL-8 (pg/mL)	77.46 [49.69 – 112.79]	111.42 [86.77 – 129.55]	110.45 [81.09 – 129.52]	124.98 [100.17 – 177.64]	0.052
IL-1β (pg/mL)	92.73 [37.81 – 271.11]^{a}	657.39 [328.83 – 1795.2]^{b}	788.24 [389.03 – 1243.36]^{b}	602.45 [329.87 – 1132.69]^{b}	<0.001

Data are presented as median [1st-3rd quartile]. Same parameters carrying different letters (a,b,c) are statistically different at p<0.05.

CAT: catalase, GPx: glutathione peroxidase, GSH: glutathione, GST: glutathione S-transferase, HGS: handgrip strength, IL: interleukin, MDA: malondialdehyde, MSWT: modified shuttle walk test, PAL: physical activity level, PCD: primary ciliary dyskinesia, SOD: superoxide dismutase.

In addition to the above findings, the correlations between the study variables were also evaluated in CF patients and the results are demonstrated in Table V. Based on the statistical analyses, GPx significantly correlated with IL-6, IL-8, and IL-1β levels (r=0.373, *p=0.046; r=0.473, *p=0.011; r=0.615, **p<0.001, respectively). There was a positive correlation between MDA and IL-6 levels (r=0.375, *p=0.045). On the other hand, a negative correlation was present between GST and IL-1β levels (r=-0.421, *p=0.026). IL-6 levels significantly correlated with IL-8 and IL-1β levels (r=0.788, **p<0.001; r=0.450, *p=0.014, respectively), while there was also a positive correlation between IL-8 and IL-1β levels (r=0.605, **p=0.001). Additionally, PAL was significantly correlated with HGS and MSWT levels (r=0.607, **p<0.001; r=0.472, **p=0.008, respectively). Furthermore, a significant positive correlation was present between HGS and MSWT levels (r=0.502, **p=0.005).

Table III. Comparison of physical activity level, handgrip strength, aerobic performance, oxidant-antioxidant, and inflammatory parameters in healthy subjects and CF patient groups based on FEV_1 z-score.

Study Parameters	Healthy Subjects (n=29)	Severe/Moderate CF Patients (n=8)	Normal CF Patients (n=20)	p value
PAL	2.33 [2 – 2.61]	1.96 [1.76 – 2.42]	2.05 [1.83 – 2.31]	0.087
HGS (kg)	24 [16.51 – 29.07]^{a}	15 [8.95 – 24.38]^{ab}	15.19 [9.62 – 22.88]^{b}	0.013
MSWT distance (m)	810 [680 - 990]	625 [522.5 - 815]	710 [642.5 – 907.5]	0.064
GSH (μg/mL)	2196.06 [390.89 – 7878.13]^{a}	6424.09 [1402.93 – 9300.86]^{ab}	7536.66 [3206.89 – 11261.22]^{b}	0.027
CAT (ng/mL)	0.23 [0.15 – 0.39]	0.35 [0.3 – 0.38]	0.27 [0.16 – 0.4]	0.324
SOD (pg/mL)	948.8 [774.67 – 1036.42]	936.27 [771.97 – 1102.12]	1042.79 [824.49 – 1160.44]	0.128
GPx (ng/mL)	3.33 [2.14 – 5.76]	2.88 [2.63 – 3.99]	2.98 [1.99 – 4.18]	0.728
MDA (ng/mL)	8599.44 [6660.51 – 10252.38]	8456.05 [6838.28 – 11178.7]	9959.45 [8165.06 – 11698.89]	0.135
GST (ng/mL)	7.94 [3.41 – 14.15]	14.03 [3.21 – 68.66]	7.68 [4.88 – 42.09]	0.503
IL-6 (pg/mL)	39.89 [17.78 – 81.44]^{a}	107.75 [11 – 198.75]^{ab}	111.45 [52.12 – 177.32]^{b}	0.015
IL-8 (pg/mL)	77.46 [49.69 – 112.79]	105.58 [27.43 – 189.63]	93.91 [41.83 – 127.29]	0.762
IL-1β (pg/mL)	92.73 [37.81 – 271.11]	88.39 [20.25 – 1131.3]	122.22 [59.56 – 820.02]	0.498

Data are presented as median [1st-3rd quartile]. Same parameters carrying different letters (a,b,c) are statistically different at $p<0.05$.

CAT: catalase, CF: cystic fibrosis, GPx: glutathione peroxidase, GSH: glutathione, GST: glutathione S-transferase, HGS: handgrip strength, IL: interleukin, MDA: malondialdehyde, MSWT: modified shuttle walk test, PAL: physical activity level, SOD: superoxide dismutase.

Note: There were two mild CF patients according to the FEV1 z-score. Therefore, this CF patient subgroup was not included in these comparisons because the number of patients needed to be increased to draw robust results.

Discussion

The study highlighted substantial alterations in homeostasis related to lung function, aerobic performance, muscle strength, inflammatory processes, and oxidant-antioxidant balance in patients with PCD and CF compared to healthy controls. The most important findings of the current study are that our results revealed an interrelated alteration between these mechanisms, potentially impacting the quality of life of patients with these rare diseases.

The involvement of the respiratory system plays a crucial role in determining the survival and quality of life of patients with PCD and CF.[25] In the present study, we determined a decrease in lung function in patients with PCD and CF relative to healthy subjects, which could be associated with limitations in

Table IV. Correlation assessment of patients with PCD in terms of physical activity level, handgrip strength, aerobic performance, oxidant-antioxidant, and inflammatory parameters.

	CAT (ng/mL)	SOD (pg/mL)	GPx (ng/mL)	MDA (ng/mL)	GST (ng/mL)	IL-6 (pg/mL)	IL-8 (pg/mL)	IL-1β (pg/mL)	PAL	HGS (kg)	MSWT distance (m)
GSH (μg/mL)	r=-0.127	r=0.261	r=0.061	r=0.404	r=-0.113	r=-0.134	r=0.003	r=-0.151	r=-0.056	r=-0.174	r=-0.357
	p=0.513	p=0.164	p=0.750	*p=0.027	p=0.551	p=0.488	p=0.988	p=0.434	p=0.772	p=0.358	p=0.053
CAT (ng/mL)		r=-0.010	r=-0.376	r=-0.223	r=-0.170	r=-0.119	r=-0.120	r=-0.323	r=-0.118	r=-0.224	r=0.273
		p=0.958	*p=0.044	p=0.246	p=0.377	p=0.545	p=0.535	p=0.093	p=0.550	p=0.242	p=0.152
SOD (pg/mL)			r=-0.069	r=0.251	r=-0.122	r=-0.081	r=-0.143	r=0.020	r=0.101	r=0.187	r=0.242
			p=0.716	p=0.181	p=0.522	p=0.677	p=0.449	p=0.919	p=0.603	p=0.323	p=0.197
GPx (ng/mL)				r=0.329	r=0.146	r=0.394	r=0.387	r=0.560	r=-0.053	r=-0.362	r=-0.308
				p=0.076	p=0.442	*p=0.034	*p=0.035	**p=0.002	p=0.783	*p=0.049	p=0.098
MDA (ng/mL)					r=0.282	r=-0.144	r=0.046	r=-0.012	r=0.015	r=-0.111	r=-0.080
					p=0.131	p=0.457	p=0.811	p=0.949	p=0.939	p=0.560	p=0.675
GST (ng/mL)						r=-0.052	r=0.292	r=-0.050	r=0.071	r=0.006	r=0.248
						p=0.787	p=0.118	p=0.796	p=0.715	p=0.974	p=0.186
IL-6 (pg/mL)							r=0.430	r=0.684	r=0.079	r=-0.123	r=0.078
							*p=0.020	**p<0.001	p=0.688	p=0.526	p=0.686
IL-8 (pg/mL)								r=0.422	r=0.145	r=0.011	r=0.083
								*p=0.023	p=0.453	p=0.954	p=0.661
IL-1β (pg/mL)									r=0.327	r=-0.095	r=0.046
									p=0.089	p=0.623	p=0.811
PAL										r=0.392	r=0.238
										*p=0.035	p=0.214
HGS (kg)											r=0.318
											p=0.087

* Correlation is significant at the 0.05 level (2-tailed).
** Correlation is significant at the 0.01 level (2-tailed).
CAT: catalase, GPx: glutathione peroxidase, GSH: glutathione, GST: glutathione S-transferase, HGS: handgrip strength, IL: interleukin, MDA: malondialdehyde, MSWT: modified shuttle walk test, PAL: physical activity level, PCD: primary ciliary dyskinesia, SOD: superoxide dismutase.

Table V. Correlation assessment of patients with CF in terms of physical activity level, handgrip strength, aerobic performance, oxidant-antioxidant, and inflammatory parameters.

	CAT (ng/mL)	SOD (pg/mL)	GPx (ng/mL)	MDA (ng/mL)	GST (ng/mL)	IL-6 (pg/mL)	IL-8 (pg/mL)	IL-1β (pg/mL)	PAL	HGS (kg)	MSWT distance (m)
GSH (μg/mL)	r=-0.211	r=0.032	r=-0.252	r=0.194	r=-0.065	r=0.044	r=-0.185	r=-0.176	r=-0.101	r=0.169	r=0.164
	p=0.263	p=0.866	p=0.187	p=0.304	p=0.739	p=0.821	p=0.337	p= 0.360	p=0.594	p=0.372	p=0.387
CAT (ng/mL)		r=-0.009	r=0.233	r=-0.247	r=0.026	r=-0.143	r=0.036	r=-0.183	r=0.196	r=0.122	r=0.231
		p=0.962	p=0.225	p=0.188	p=0.895	p=0.458	p=0.853	p=0.341	p=0.300	p=0.521	p=0.220
SOD (pg/mL)			r=-0.181	r=-0.266	r=0.358	r=-0.308	r=-0.259	r=-0.215	r=0.264	r=0.267	r=0.102
			p=0.5348	p=0.156	p=0.056	p=0.104	p=0.176	p=0.263	p=0.158	p=0.154	p=0.592
GPx (ng/mL)				r=-0.090	r=0.336	r=0.373	r=0.473	r=0.615	r=0.075	r=-0.058	r=0.064
				p=0.644	p=0.081	*p=0.046	*p=0.011	**p<0.001	p=0.698	p=0.763	p=0.743
MDA (ng/mL)					r=-0.087	r=0.375	r=0.351	r=0.167	r=-0.319	r=-0.239	r=-0.109
					p=0.653	*p=0.045	p=0.062	p=0.388	p=0.086	p=0.204	p=0.567
GST (ng/mL)						r=-0.189	r=-0.317	r=-0.421	r=0.231	r=-0.105	r=0.076
						p=0.336	p=0.100	*p=0.026	p=0.228	p=0.588	p=0.695
IL-6 (pg/mL)							r=0.788	r=0.450	r=-0.086	r=0.070	r=0.040
							**p<0.001	*p=0.014	p=0.657	p=0.719	p=0.838
IL-8 (pg/mL)								r=0.605	r=0.1027	r=0.150	r=0.101
								**p=0.001	p=0.889	p=0.436	p=0.602
IL-1β (pg/mL)									r=0.012	r=0.051	r=-0.159
									p=0.952	p=0.794	p=0.410
PAL										r=0.607	r=0.472
										**p<0.001	**p=0.008
HGS (kg)											r=0.502
											**p=0.005

* Correlation is significant at the 0.05 level (2-tailed).
** Correlation is significant at the 0.01 level (2-tailed).
CAT: catalase, CF: cystic fibrosis, GPx: glutathione peroxidase, GSH: glutathione, GST: glutathione S-transferase, HGS: handgrip strength, IL: interleukin, MDA: malondialdehyde, MSWT: modified shuttle walk test, PAL: physical activity level, SOD: superoxide dismutase.

exercise capacity, muscle strength, increased inflammatory responses, and imbalances in oxidant-antioxidant mechanisms.

The current investigation evidenced a reduction in the MSWT distance in patients with severe/moderate PCD compared to their healthy peers despite similar PAL levels. Similarly, Madsen et al.[7] reported that the aerobic fitness of PCD patients was lower than that of healthy subjects. This impaired aerobic capacity in PCD patients is probably due to reduced respiratory functions and increased inflammation. In addition, the MSWT level of CF patients was lower compared to healthy subjects, although this difference was insignificant. In literature, Leite et al.[26] demonstrated that children with CF had functional limitations in the MSWT distance.

Additionally, HGS levels were lower in both mild PCD and normal CF patients compared to the healthy subjects. Similar to our results, Sahlberg et al.[27] found that muscle strength and function decreased in CF patients compared to control subjects. Another study in the literature showed that PCD patients had lower handgrip strength than control subjects.[28] Muscle weakness in these patients could be related to a combination of factors, including nutritional status, airway obstruction, impaired aerobic capacity, inactivity, systemic inflammation, and oxidative stress. Importantly, MSWT distance was positively related to HGS level in CF patients in the current study. Similarly, Wells et al.[29] stated that there was a positive correlation between HGS and peak aerobic power (VO_2 peak) in children with CF. However, Cardoso et al.[30] reported no significant relationship between HGS and MSWT in children and adolescents with CF. This difference may be due to the body composition, including growth, weight, and height, which are related to muscle strength and MSWT performance in CF. In addition, previous investigations involving PCD patients have not yet explored this specific correlation.

Although PCD and CF have different genetic and functional origins, patients suffer from recurrent infections due to impaired cilia functions and mucus accumulation.[4,5] In addition, cystic fibrosis is included in the subgroup of immunodeficiency motility disorders, in which monocytes are affected, and chemotaxis is impaired.[31–33] In the literature, it has been reported that cytokines have a crucial role in inflammatory responses during infection.[34] Monocytes of PCD patients produced significantly more IL-1β than healthy individuals when stimulated with bacterial products (i.e., lipopolysaccharide and peptidoglycan).[12] Shoemark et al.[35] reported that IL-6, IL-8, and TNF-α levels were significantly higher in nasal samples of PCD patients than in controls. However, to the best of our knowledge, only one study has considered blood biomarkers of inflammation in PCD patients. In that study, Marino et al.[36] showed that the mean plasma concentrations of IL-1β, IL-2, IL-6, IL-8, and TNF-α in PCD patients and these cytokines were not increased in their cohort compared to available normative data.[37,38] On the other hand, it was stated that the serum levels of IL-6 and IL-1β were higher in patients with CF compared to controls.[39,40] According to our plasma results, IL-6 levels were higher in normal PCD and CF patients than in healthy subjects. On the other hand, IL-1β levels were higher in PCD patients than in healthy subjects, while IL-8 levels in PCD patients tended to be higher compared to healthy subjects. Moreover, there was a positive relationship between IL-8 and IL-1β in PCD and CF patients. Furthermore, IL-6 was significantly related to IL- 8 and IL-1β in the patient groups.

Many biomarkers of the oxidant-antioxidant system that may be useful in better understanding and managing these patients were evaluated in the current study. As a result, SOD levels were higher in severe/moderate PCD patients compared to healthy subjects while GSH levels were higher in normal CF patients than in healthy subjects. The other antioxidant parameters, such as CAT, GSH,

and GPx levels were also increased in patients with PCD compared to healthy controls, although these differences were not statistically significant. Given these results, we could speculate that increased chronic inflammation may trigger antioxidant mechanisms in the PCD patients. Oxidative stress is characterized as an imbalance between the antioxidant and oxidant systems, and it has rarely been studied in PCD. Zihlif et al.[41] stated that oxidative stress, as shown by 8-isoprostane, increased in the exhaled breath condensate of PCD children compared to healthy subjects. Additionally, Reula et al.[42] investigated the oxidative stress status in ciliated nasal epithelial cells (CNEC) from patients with PCD. As a result of the study, reduced GSH and total superoxide (O2-) were higher, and nitric oxide (NO) levels were lower in PCD patients than in PCD-like and the control group. Nevertheless, no significant alteration was observed in the oxidative damage in lipids and proteins of PCD and PCD-like patients compared to the control group. On the contrary, oxidative stress has been widely investigated in CF disease.[43–45] Olveira et al.[43] evaluated various oxidation biomarkers in plasma samples of 36 CF and 41 controls. Accordingly, CF patients' CAT, 8-isoprostanes, and thiobarbituric acid reactive substances [TBARS] levels were higher, but SOD levels were lower than controls. Another study determined that the plasma GPx levels were higher in 76 CF patients than in 40 control subjects. On the other hand, SOD activity in red blood cells was not different among study groups.[44] Galiniak et al.[45] reported that 42 CF patients' serum MDA levels were higher than 16 controls. In another study, GST activity was not different in 36 CF patients compared to 9 healthy subjects.[46] Another marker they studied was GSH, which is one of the main reactive oxygen species neutralization mechanisms. According to the results, in the presence of *P. aeruginosa* infection (n=12), the GSH level was similar to that of the healthy subjects (n=9). On the other hand, uninfected CF children's (n=24) GSH content was significantly decreased compared to controls (n=9).[46] From this perspective, it should not be overlooked that findings related to the antioxidant activities of CF patients could be affected by many factors, including accompanying diseases and clinical conditions such as disease severity and bacterial infections.

Another feature of our study was determining the correlation between the study groups' oxidative stress and inflammation parameters. The literature shows strong evidence that oxidative stress and inflammation are tightly related processes.[47] Similarly, our correlation findings support the interdependence between these pathophysiological processes. For instance, GPx was significantly related to IL-8, IL-6, and IL-1β levels in PCD and CF patients.

Our study has several limitations. Firstly, it was a single-center study, which limits the generalization of the results. Secondly, larger sample sizes may be needed to evaluate the statistical differences further. Thirdly, participants were selected by the study team, which may have led to selection bias. Finally, radiological findings could not be included in the study because not all patients had a thorax computed tomography. Despite these limitations, the study's strength is that these mechanisms have been considered together in pediatric patients with PCD and CF for the first time.

Conclusion

The processes including clinical findings, functional exercise capacity, muscle strength, oxidant-antioxidant balance, and inflammation were affected in PCD and CF patients. These alterations could be linked to each other through cause-and-effect relationships. It is crucial to know the cause-and-effect relationships in disease to improve treatment outcomes and develop a comprehensive perspective on the pathogenesis of the disease. In this study, impaired lung function could result in decreased physical capacity and muscle strength, as well as changes in the inflammatory and oxidant-antioxidant systems. On the other hand, the imbalance in the oxidant-antioxidant

equilibrium and inflammatory response, which are closely related, may potentially affect muscle weakness and physical performance. Hopefully, our multifactorial findings may provide a new perspective for future studies of these rare diseases to understand the underlying mechanisms of diseases and contribute to finding new therapeutic approaches. In addition, our findings have to be confirmed by larger-scale, multicenter studies.

Ethical approval

The present study was approved by Hacettepe University Noninterventional Clinical Research Ethics Committee with approval no: GO 18/194 on 13 February 2018.

Author contribution

Study conception and design: YK, CBO, HSU, DII, UO, MTB, HA, GG, SS; data collection: YK, CBO, HSU, AC, DAT, SEP, MH, UO; analysis and interpretation of results: YK, SS, GG, MTB, UO, DII, SK; draft manuscript preparation: YK, DAT. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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