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Investigation of respiratory muscle strength and its influence on exercise capacity and quality of life in patients with idiopathic pulmonary fibrosis

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Abstract. *Background:* Adequate respiratory muscle strength is required to meet the increased ventilatory demand during physical activities. However, it is not well known whether respiratory muscle strength is impaired in patients with idiopathic pulmonary fibrosis (IPF). *Objectives:* This study aimed to investigate the relationship between respiratory muscle strength and exercise capacity, quality of life, physical activity level, and fatigue in IPF patients. *Methods:* The study comprised 30 individuals with idiopathic pulmonary fibrosis (IPF) and 30 healthy controls. Maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) were measured to assess respiratory muscle strength. The International Physical Activity Questionnaire-Short Form, 6-minute walk test distance (6MWD), St George Respiratory Questionnaire (SGRQ), and Fatigue Severity Scale (FSS) were employed to evaluate physical activity level, exercise capacity, quality of life, and fatigue severity, respectively. *Results:* MIP (81±29 vs.73±20 cmH_2O) and MEP (93±31 vs. 93±34 cmH_2O) did not differ significantly between IPF patients and controls ($p>0.05$). In patients with IPF, MIP was significantly correlated with 6MWD ($r=0.533$), SGRQ ($r=-0.428$), and FSS ($r=-0.433$). Multivariate models including MIP, MEP, FEV_1, FVC, and PA level explained 74% of the variance in the 6MWD ($p<0.001$), and MIP, FEV_1, and PA level were independent predictors of the 6MWD, with FEV_1 being the strongest predictor ($\beta=0.659$). Multivariate models predicting SGRQ revealed none of MIP, FEV_1 or PA level was directly influencing the SGRQ score. *Conclusions:* This study suggests that patients with IPF do not have respiratory muscle weakness. Inspiratory muscle strength has a direct influence on exercise capacity but an indirect effect on quality of life, probably by influencing exercise capacity.

Key words: idiopathic pulmonary fibrosis, interstitial lung diseases, physical activity, maximal inspiratory pressure, six-minute walking test

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Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic progressive disease characterized by the development of fibrotic tissue in the lungs (1). The development of fibrotic tissue in the lungs leads to impaired lung function and respiratory failure (2).

The involvement of respiratory muscles in patients with interstitial lung disease remains unclear,

although studies suggest that there may be weakness in the respiratory and peripheral muscles (3). On the other hand, studies have reported that while diaphragm strength is decreased in these patients, global respiratory muscle strength is similar to that in healthy individuals (2). These discrepancies may be due to differences in study design, patient populations, or measurement techniques, and further research is needed to clarify the relationship between respiratory muscle weaknesses in IPF.

Respiratory muscle strength is a variable that can affect a patient's clinical status and quality of life, especially in patients with reduced lung reserve. Several studies have suggested that respiratory muscle strength may be associated with gas exchange (4), exercise capacity (5), and cough strength (6) in various patient groups. Some studies have shown that an increase in respiratory muscle strength can have a positive impact on exercise capacity (7), lung volumes, and quality of life (QOL) (8). However, the number of studies examining the relationship between respiratory muscle strength, quality of life, and exercise capacity in individuals with IPF are extremely limited.

Although the results of the study comparing the respiratory muscle strength of IPF cases and healthy controls differ, an increase in exercise capacity has been reported to reduce dyspnea and improve QOL (9). When examining the health-related QOL of IPF patients, it has been shown that general health, energy level, respiratory symptoms, and level of independence all have an impact. However, the exercise limitation seen in IPF cases cannot be explained only by dyspnea and respiratory function (10).

In this study, we aimed to compare respiratory muscle strength in a cohort of IPF patients and healthy controls using multiple measures of respiratory muscle function, including Maximal Inspiratory Pressure (MIP) and Maximal Expiratory Pressure (MEP). We also aimed to investigate how respiratory muscle strength affects exercise capacity and quality of life and to identify the factors determining exercise capacity and quality of life.

Methods

A case-control study was conducted. The study was approved by the Istanbul Training and Research Hospital Clinical Research and Ethics Committee (Protocol Number: 1357) and prospectively registered on the ClinicalTrial.gov website (registration number: NCT03588260). This study was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from each participant.

Respiratory muscle strength, exercise capacity, dyspnea level, physical activity, and QOL were measured in two groups: patients with interstitial pulmonary fibrosis and healthy volunteers of similar age and demographic features. The inclusion criteria for the IPF group were being between the ages of 40-80 years, having a diagnosis of IPF according to the clinical diagnostic criteria of the American Thoracic and European Respiratory Societies (1), and being in a stable clinical state at the time of inclusion without infection or exacerbation in the previous 4 weeks. Exclusion criteria for the IPF group included a history of exertional syncope, any concurrent illness that could impede exercise testing (such as severe orthopedic problems, neurological disorders, neuromuscular diseases, unstable heart conditions, pulmonary hypertension, and flow-limiting coronary artery disease etc.), and inability to comply with respiratory function tests and mouth pressure measurement.

The inclusion criterion for the healthy group was the absence of chronic health problems. The exclusion criterion for this group was inability to comply with pulmonary function tests and mouth pressure measurements.

Outcome measurements

Respiratory muscle strength: Inspiratory muscle strength was evaluated by measuring maximum inspiratory pressure (MIP), and expiratory muscle strength was evaluated by measuring maximum expiratory pressure (MEP) using a Pony Fx instrument (Cosmed, Italy). The patient placed a rubber mouthpiece with flanges on the device, sealed their lips firmly around the mouthpiece, exhaled/inhaled slowly and completely, and then tried to breathe as hard as possible (11). The patient was allowed to rest for approximately one minute, and the maneuver was repeated until the peak value was achieved. Verbal or visual feedback was provided after each maneuver, and the aim was to achieve a variability

between measurements of less than 5 cm H_2O. The maximum value was recorded (12). MIP values below 80 cmH_2O were considered inspiratory muscle weakness (13).

Pulmonary function test: It was conducted by using the Pony Fx instrument (Cosmed, Italy) according to the American Thoracic Society (ATS) guidelines (14).

Six minute walking test: The test was conducted in a 30-meter corridor in accordance with the American Thoracic Society (ATS) guidelines. Patients were instructed to walk as fast as they can. Before and after the test, oxygen saturation, heart rate, Borg fatigue rating, and walking distance were recorded (15, 16). The walking distance was recorded in the test and also expressed as a percentage of the predictive value (17).

Saint George Respiratory Questionnaire: The Saint George Respiratory Questionnaire (SGRQ) was used to assess the health-related quality of life (HRQL) of participants. The questionnaire consists of 50 items, which are divided into three domains: symptoms, activity, and impact. The scores for each domain are combined to obtain a total score, which ranges from 0 to 100, with higher scores indicating worse HRQL. The Turkish version of the SGRQ was used, which has been shown to have good reliability and validity in previous studies(18).

International Physical Activity Questionnaire Short Form: The International Physical Activity Questionnaire Short Form (IPAQ-SF) was used to assess physical activity levels over the past seven days. The questionnaire consists of seven items and assesses the frequency and duration of physical activity in three domains: work-related physical activity, physical activity during leisure time, and domestic and transportation-related physical activity. The total amount of physical activity participation was calculated as MET.min/week value by summing the scores for all three domains (19).

Fatigue Severity Scale: The Fatigue Severity Scale (FSS) is a self-report questionnaire used to assess the severity of fatigue experienced by individuals. It consists of nine items that measure the impact of fatigue on various aspects of a person's life. Each item is scored on a scale from 1 to 7, with higher scores indicating more severe fatigue (20).

Statistical analysis

Data was analyzed using SPSS v.20 (IBM Corp., Armonk, NY). Normality of the data was explored using Kolmogorov-Smirnov test; the total amount of physical activity as MET.min/wk showed non-normal distribution showed non-normal distribution so it was handled with non-parametric tests. Comparison between IPF patients and healthy controls was conducted using Independent Samples T-test or Mann Whitney U test for numeric variables and Chi-square test for categorical variables. Correlations among the measured variables in IPF patients were analyzed using Pearson or Spearman's rank correlation analysis. For exploring the independent predictors of exercise capacity and QOL in IPF patients, multivariate regression models were created including the respiratory muscle strength, pulmonary function and physical activity level as independent variables, and backward stepwise selection was performed for creating subsequent models. Since FVC showed relatively high multicollinearity in the regression models (VIF=3.5-4.5), only FEV_1 was included in the models as an indicator of pulmonary function. $P<0.05$ was considered statistically significance for all analyses.

In the literature, it is reported that there is a moderate association between MIP value and maximal exercise capacity metrics in patients with interstitial lung diseases (21). Accordingly, we hypothesized to detect a moderate correlation, with a correlation coefficient of 0.5, between MIP value and 6MWD in our study as well. To be able to detect such correlation with 80% power at 95% confidence level, it was calculated that 30 participants should be included in the IPF cohort in the study (22). Then, an equal number of healthy volunteers were included in the study as well to be able to compare the clinical metrics of IPF patients.

Results

Demographics and clinical characteristics of IPF patients and healthy controls are shown in Table 1. Groups were similar in terms of demographical features including age, gender and body mass index ($p>0.05$).

Comparison of respiratory muscle strength, pulmonary function, exercise capacity and physical activity level between IPF patients and healthy controls are shown in Table 2. Respiratory muscle strength was similar in IPF patients and healthy controls. Number of cases having a MIP values below 80 cmH_2O in IPF patients and healthy controls were also similar. Among the measured variables, only FEV_1 and FVC were significantly different between groups, favoring healthy controls (p<0.001).

Association of respiratory muscle strength with pulmonary function, exercise capacity, physical activity level, QOL and fatigue metrics in IPF patients are shown in Table 3. MIP demonstrated a significant correlation to FEV_1, FVC, 6MWD, PA level, SGRQ total score and FSS score, with 6MWD was being the strongest correlate of MIP (r=0.553; p<0.01). MEP did not correlate to any of the measured variables (p>0.05). Comparison of 6MWD and SGRQ total score between the IPF patients with MIP values below and above 80 cmH_2O is shown in Figure 1. IPF patients with inspiratory muscle weakness (MIP<80 cmH_2O) had significantly worse 6MWD (326±155 vs 522±160 m) and SGRQ total score (60±19 vs 41±17) compared to those do not have inspiratory muscle weakness (p<0.01).

Multivariate models for exploring the independent predictors of exercise capacity measured by 6MWD in IPF patients are shown in Table 4. Model 1 including MIP, MEP, FEV_1, FVC and PA level was able to explain 74% variance in 6MWD (p<0.001), and MIP, FEV_1 and PA level were independent predictors of 6MWD. Model 2, which was created with backward stepwise selection, including MIP, FEV_1 and PA level was able to explain 66% of variance in 6MWD, which was statistically significant as well (p<0.001). However, in this model, MIP was not an independent predictor of 6MWD compared to FEV_1 and PA level. Subsequent models revealed that FEV1 was the strongest predictor of 6MWD, followed by PA level.

Multivariate models for exploring the independent predictors of QOL measured by SGRQ total score in IPF patients are shown in Table 5. Model 1 including MIP, MEP, FEV_1, FVC and PA level was able to explain 32% of variance in SGRQ total score; however, the model was statistically insignificant. Model 2 including MIP, FEV_1 and PA level was able to significantly explain 30% of variance in SGRQ total score (p=0.021); however, none of the variables in the model was an independent predictor

Table 1. Demographics and clinical characteristics of IPF patients and controls.

	IPF patients (n=30)	Healthy Controls (n=30)
Gender (male)	25 (83%)	20 (67%)
Age (years)	67.13±7.21	65.43±6.97
BMI (kg/m^2)	26.82±3.22	26.30±2.87
SGRQ total (0-100)	49.21±19.99	
FSS (9-63)	35.87±18.07	

Abbreviations: BMI: Body mass index, FSS: Fatigue Severity Scale, IPF: Idiopathic pulmonary fibrosis, SGRQ: St. George Respiratory Questionnaire.

Table 2. Comparison of respiratory muscle strength, pulmonary function, exercise capacity and physical activity level between IPF patients and controls.

	IPF patients (n=30)	Healthy Controls (n=30)	P value	Effect size (*d*)
MIP (cmH_2O)	81.00±28.49	72.73±20.24	0.200	0.33
MIP <80 cmH_2O (n)	13 (47%)	17 (53%)	0.439	
MEP (cmH_2O)	93.30±31.46	92.87±33.65	0.959	0.03
FEV_1 (pred%)	66.35±17.34	86.97±23.02	<0.001	1.04
FVC (pred%)	63.83±16.74	92.20±23.28	<0.001	1.39
6MWD (m)	437±184	488±46	0.152	0.09
6MWD (pred%)	87.47±36.12	97.30±12.98	0.169	0.35
PA (MET-min/week)	214 [195-1221]	174 [264-828]	0.666	0.15

Data is reported as mean±standard deviation, n (%) or median [95% CI]. Abbreviations: FEV1: Forced expiratory volume in 1 s, FVC: Forced vital capacity, IPF: Idiopathic pulmonary fibrosis, MEP: maximum expiratory pressure, MIP: Maximum inspiratory pressure, PA: Physical activity level, 6MWD: 6-min walk test distance

for SGRQ total score, indicating these three variables affect QOL only by influencing other variables. For further exploring this interaction, a new model (model 3) was created by adding 6MWD in a model alongside MIP, FEV_1 and PA. This new model was able to significantly explain 44% of variance in SGRQ total score and revealed that 6MWD was an independent predictor for SGRQ compared to MIP, FEV_1 and PA level. Considering MIP is significantly associated with both 6MWD and SGRQ (Table 3), results of the model 3 may be interpreted as MIP does not directly affect QOL but by influencing exercise capacity.

Table 3. Association of MIP and MEP with pulmonary function, exercise capacity, physical activity, quality of life and fatigue severity metrics in IPF patients (n=30).

	MIP	MEP
FEV_1 (pred%)	0.437*	0.122
FVC (pred%)	0.472**	0.123
6MWD (m)	0.553**	0.091
PA (MET-min/week)	0.491**	0.280
SGRQ (0-100)	-0.428*	-0.253
FSS (9-63)	-0.433*	-0.327

Correlation coefficients (r or rs) are presented: *p<0.05 and **p<0.01. Abbreviations: FEV1: Forced expiratory volume in 1 s, FSS: Fatigue Severity Scale, FVC: Forced vital capacity, IPF: Idiopathic pulmonary fibrosis, MEP: maximum expiratory pressure, MIP: Maximum inspiratory pressure, PA: Physical activity level, SGRQ: St. George Respiratory Questionnaire, 6MWD: 6-min walk test distance

Discussion

Our study demonstrated that respiratory muscle weakness was not present in all IPF patients. Also, the exercise capacity of IPF patients does not seem to be severely impaired compared to their healthy counterparts. However, MIP value was a significant predictor for exercise capacity in these patients; patients having a higher MIP value had better exercise capacity. On the other hand, MIP value did not have a direct effect on quality of life, but an indirect effect by influencing exercise capacity. MEP value was not a significant correlate of neither exercise capacity nor quality of life. Our results suggest that close monitoring of inspiratory muscle strength may help maintain an adequate level of exercise capacity throughout the disease process in IPF patients.

In patients with IPF, respiratory function tests reveal a restrictive pattern anomaly due to diffuse fibrotic tissue in the lungs (23). The extent to which respiratory muscle strength is affected by the current

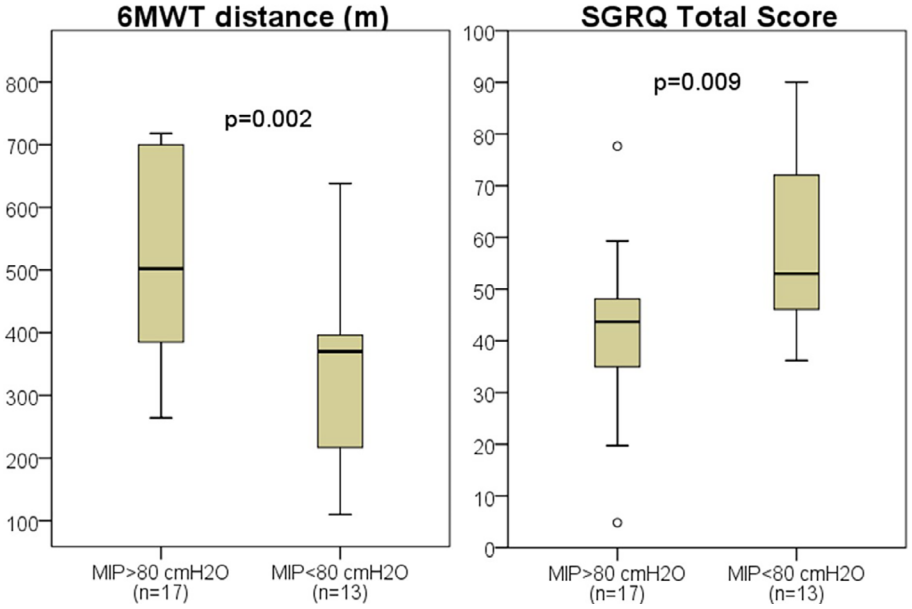

Figure 1. Comparison of 6MWD and SGRQ total score between the IPF patients with MIP values below and above 80 cmH_2O.

Table 4. Multivariate analysis for exploring the independent predictors of exercise capacity (6MWD) in IPF patients (n=30).

	B	Std Error	Std. β	p	R	R^2	Adj. R^2	VIF
Model 1				<0.001	0.844	0.713	0.667	
(Constant)	20.320	95.819		0.834				
MIP	2.536	0.861	0.392	0.007				1.539
MEP	-1.667	0.743	-0.284	0.034				1.397
FEV_1	4.958	1.294	0.466	0.001				1.289
PA	0.055	0.016	0.407	0.002				1.181
Model 2				<0.001	0.810	0.655	0.616	
(Constant)	-87.939	88.999		0.332				
MIP	1.709	0.836	0.264	0.051				1.257
FEV_1	5.371	1.377	0.505	0.001				1.263
PA	0.044	0.016	0.326	0.011				1.068
Model 3				<0.001	0.775	0.600	0.570	
(Constant)	-29.073	89.033		0.747				
FEV_1	6.526	1.327	0.613	<0.001				1.050
PA	0.048	0.017	0.357	0.008				1.050
Model 4				<0.001	0.692	0.478	0.460	
(Constant)	-50.304	99.488		0.617				
FEV_1	7.358	1.452	0.692	<0.001				

Abbreviations: FEV_1: Forced expiratory volume in 1 s, FVC: Forced vital capacity, IPF: Idiopathic pulmonary fibrosis, MEP: maximum expiratory pressure, MIP: Maximum inspiratory pressure, PA: Physical activity level, VIF: Variance inflation factor, 6MWD: 6-min walk test distance

Table 5. Multivariate analysis for exploring the independent predictors of quality of life (SGRQ total score) in IPF patients (n=30).

	B	Std Error	Std. β	p	R	R^2	Adj. R^2	VIF
Model 1				0.044	0.560	0.314	0.204	
(Constant)	96.560	16.054		<0.001				
MIP	-0.145	0.144	-0.207	0.323				1.539
MEP	-0.061	0.124	-0.096	0.628				1.397
FEV_1	-0.443	0.217	-0.384	0.052				1.289
PA	-0.001	0.003	-0.048	0.790				1.181
Model 2				0.021	0.555	0.307	0.228	
(Constant)	92.595	13.669		<0.001				
MIP	-0.176	0.128	-0.250	0.183				1.257
FEV_1	-0.428	0.211	-0.371	0.054				1.263
PA	-0.001	0.002	-0.076	0.657				1.068
Model 3				0.005	0.662	0.438	0.348	
(Constant)	86.724	12.787		<0.001				
MIP	-0.062	0.127	-0.088	0.632				1.459
FEV_1	-0.069	0.244	-0.060	0.780				2.002
PA	0.002	0.003	0.125	0.483				1.377
6MWD	-0.067	0.028	-0.616	0.023				2.901

Abbreviations: FEV1: Forced expiratory volume in 1 s, FVC: Forced vital capacity, IPF: Idiopathic pulmonary fibrosis, MEP: maximum expiratory pressure, MIP: Maximum inspiratory pressure, PA: Physical activity level, SGRQ: St. George Respiratory Questionnaire, VIF: Variance inflation factor, 6MWD: 6-min walk test distance.

clinical condition is a matter of debate. In a case report involving long-term combined training including aerobic and strengthening, it was reported that the average baseline MIP values of IPF patients were 110% of the predicted values, and an increase in respiratory muscle strength was observed following the training (24). In a study comparing respiratory muscle strength among different patient groups, it was reported that the MIP value of the IPF group was 99.9% of the expected (4). On the other hand, in a study comparing clinical parameters with healthy controls, the MIP values of IPF patients were measured at 37%, and there was no statistical difference compared to the control group (25). Consistent with the literature, we found that IPF patients do not have respiratory muscle weakness despite having impaired spirometric parameters. This may suggest that the altered lung mechanics in our patient group have not yet affected the respiratory muscles. On the other hand, it is reported that stiffness of the lungs in interstitial lung diseases increases the work of breathing, and this may constitute a resistance training effect on respiratory muscles (2). This "pseudo" training as well may help explain how IPF patients retain their normal MIP and MEP values.

In a patient-reported study involving individuals with Idiopathic Pulmonary Fibrosis (IPF), both exercise capacity and disease symptoms emerged as independent risk factors for mortality. Notable symptoms included the use of supplemental oxygen, decreased forced vital capacity, and reduced carbon monoxide diffusing capacity (26). Similarly, another study emphasized the significance of insufficient exercise capacity, elevated levels of dyspnea, and abnormal ventilatory response as predictors of poorer survival outcomes (27). Furthermore, a study investigating respiratory and peripheral muscle strength in Chronic Obstructive Pulmonary Disease (COPD) patients revealed a direct correlation between decreased muscle strength and worsened exercise capacity and functional limitations (28). Moreover, sarcopenia, a condition characterized by loss of muscle mass and function, is commonly observed in chronic respiratory diseases, exerting detrimental effects on muscle strength and, consequently, exercise capacity (29). This condition may also manifest in fibrotic lung patients in advanced disease stages, particularly those who are physically inactive (30, 31). However, no evaluation regarding sarcopenia could be made in our study.

In our study, we examined the factors associated with exercise capacity in IPF patients. Regression models created to identify the independent predictors of exercise capacity in IPF patients revealed that inspiratory muscle strength directly influences exercise capacity, but FEV_1 emerged as the strongest predictor of exercise capacity compared to other variables in the models. The fact that MIP is normal but FEV_1 is impaired in IPF patients may help explain why FEV_1 is a stronger predictor of exercise capacity in these patients. It is not surprising that FEV_1 has the strongest influence on exercise capacity. In a study delving into the correlation between exercise capacity and spirometric measurements, researchers reported that chronic hypoxia could be one of the factors contributing to the simultaneous decline in FEV_1 and exercise capacity (32). Additionally, another study exploring the interplay between perceived dyspnea, leg exertion during exercise, FEV_1, and airway limitation highlighted the significant roles of both leg muscle strength and FEV_1 in influencing dyspnea severity and leg fatigue. Consequently, individuals with lower FEV_1 levels tend to experience heightened dyspnea, negatively impacting exercise performance (33).

Although the FEV_1 was the strongest contributor, MIP had a significant influence on exercise capacity as well in our study. Several mechanisms may help explain the association between MIP and exercise capacity. In IPF patients, excessive dead space ventilation leads to an increased metabolic energy demand of the respiratory muscles, which can exceed 50% of the total body oxygen delivery. As a result, insufficient energy is provided to the non-respiratory muscles supporting locomotion, leading to energy deficiency and exercise intolerance (34). In a study where the respiratory muscle load was alleviated during submaximal exercise through non-invasive ventilation, an increase in endurance time, arterial hemoglobin saturation, and a decrease in breathlessness were observed (35). This as well highlights the relationship between respiratory muscles and exercise capacity. In a study investigating the impact of respiratory muscle strength on the benefits of pulmonary rehabilitation, it was reported that individuals with lower inspiratory muscle strength experience more severe dyspnea and lower dose-response relationship physical activity and exercise capacity. Furthermore, an increase in respiratory muscle strength was found to be associated with an improvement in

exercise capacity (36). In another study involving end-stage lung transplant candidates, the group that received inspiratory muscle training (IMT) demonstrated a greater increase in 6MWD compared to the control group that did not receive IMT (7). We believe this strong interaction between inspiratory muscle strength and exercise capacity highlights the importance of preservation of the inspiratory muscle strength for maintaining an acceptable level of exercise capacity.

Another factor influencing the exercise capacity in IPF patients in our study was PA level. In a study examining the impact of daily PA levels on exercise capacity in IPF, regression analysis revealed that the 6-minute walk distance was influenced by vital capacity, quadriceps femoris muscle strength, and PA level (37). Similarly, in a study investigating the relationship between daily PA levels and the 6-minute walk distance in patients with fibrotic idiopathic interstitial pneumonia, it was found that daily step count correlated with diffusion capacity, forced vital capacity (FVC), and the 6-minute walk distance (38). It is even reported that 6MWD correlates more strongly with measures of peak work capacity and physical activity than with respiratory function in various chronic lung diseases, emphasizing the association of PA level and exercise capacity (39). Routine PA participation is proven to be associated with a marked reduction in all-cause mortality in over 25 chronic diseases including chronic lung diseases. Many of the health benefits of PA are originated from its positive effects on cardiovascular fitness. There is a dose relationship between PA level and its benefits. Even a little amount of physical activity can provide significant health benefits (40). This may help explain why we found a strong association between PA level and exercise capacity, even though the PA level is rather low in our patients.

Progressive loss of respiratory function and exercise capacity in IPF patients results in a decrease in QOL. In a study where IPF patients were followed for 12 months, it was reported that QOL was associated with lung function, comorbidities, disease duration, and patient clinical characteristics (41). In our study, we found that inspiratory muscle strength, FEV_1, and PA level significantly correlate to QOL in these patients. However, they were not directly influencing QOL, but rather indirectly by influencing exercise capacity. Exercise capacity was the main predictor for QOL in our study. Although our study did not find MIP to be an independent predictor of QOL, there are studies in the literature that demonstrate a relationship between MIP and QOL. In a study conducted on patients with amyotrophic lateral sclerosis, researchers found that individuals with lower QOL scores exhibited significantly lower MIP values. Lower MIP values were associated with lower scores in all domains of the Short Form-36 questionnaire except for pain and physical components (42). Another study focused on patients with chronic kidney disease who received IMT reported an improvement in their quality of life following the intervention (43). While various mechanisms have been proposed to explain this improvement in different studies, the general consensus is that IMT reduces dyspnea during physical exertion, increases energy levels, and decreases fatigue during activity (44, 45). Exercise plays an important role in the intra and extra-pulmonary complex pathophysiological processes of IPF. Exercise exerts a positive effect on pathological abnormalities and deficiencies through its chronic physiological stimulus on the cardiovascular, pulmonary, and musculoskeletal systems (46). Studies have shown that there is a parallel between the decrease in exercise capacity and the decline in quality of life. This indicates that the decrease in exercise capacity is known to be associated with a decrease in QOL in these studies (46). Functional capacity is the ability to perform activities of daily living that require sustained aerobic metabolism. Most daily activities do not require maximal effort, thus the submaximal exercise capacity metrics such as 6MWD provide reliable estimates for a person's ability to perform these activities (47, 48). Considering the ability to perform daily activities is one of the main components of the QOL concept (49, 50), it is not surprising to detect a strong association between 6MWD and QOL in IPF patients as well. Taking into account the potential of MIP to affect exercise capacity and consequently, quality of life, preserving respiratory muscle strength in these patients will also contribute to maintaining their quality of life.

Our study has several limitations. Firstly, we were unable to conduct stratified sampling to include IPF patients from each clinical stage and in equal numbers in our cohort due to the heterogeneous nature of IPF cases and the relatively low number of IPF patients followed up in our clinic. Comparing the respiratory muscle function among different stages of IPF patients may help better investigate the involvement of

respiratory muscles in this disease. Another limitation is that we assessed respiratory muscle strength solely by measuring MIP and MEP. It has been reported in the literature that measuring vital capacity in sitting and supine positions is a qualified measure to demonstrate diaphragm dysfunction (51). The reason for this is the availability of only a mouth pressure measurement device in our clinic.

As a conclusion, the study indicates that IPF patients do not have respiratory muscle weakness. However, inspiratory muscle strength has a direct influence on exercise capacity in these patients, indicating that inspiratory muscle strength should be monitored and addressed as well throughout the disease process for preserving the exercise capacity. Inspiratory muscle weakness in these patients may also result in impaired QoL since exercise capacity is one of the most important determinants of QoL, which further emphasize the close monitorization of inspiratory muscles.

Ethics Committee Approvement: Istanbul Education and Research Hospital Clinical Research Ethics Committee, (Number 1357). Clinical trial registration: NCT03588260.

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References

1. Raghu G, Remy-Jardin M, Myers JL, et al. Diagnosis of Idiopathic Pulmonary Fibrosis. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med 2018;198:e44-e68.
2. Walterspacher S, Schlager D, Walker DJ, Muller-Quernheim J, Windisch W, Kabitz HJ. Respiratory muscle function in interstitial lung disease. T Eur Respir J 2013;42:211-9.
3. Panagiotou M, Polychronopoulos V, Strange C. Respiratory and lower limb muscle function in interstitial lung disease. Chron Respir Dis 2016;13:162-72.
4. Nishimura Y, Hida W, Taguchi O, et al. Respiratory muscle strength and gas exchange in neuromuscular diseases: comparison with chronic pulmonary emphysema and idiopathic pulmonary fibrosis. Tohoku J Exp Med 1989;159:57-68.
5. Aslan GK, Akinci B, Yeldan I, Okumus G. Respiratory muscle strength in patients with pulmonary hypertension: The relationship with exercise capacity, physical activity level, and quality of life. Clin Respir J 2018;12:699-705.
6. Kang SW, Shin JC, Park CI, Moon JH, Rha DW, Cho DH. Relationship between inspiratory muscle strength and cough capacity in cervical spinal cord injured patients. Spinal cord 2006;44:242-8.
7. Pehlivan E, Mutluay F, Balci A, Kilic L. The effects of inspiratory muscle training on exercise capacity, dyspnea and respiratory functions in lung transplantation candidates: a randomized controlled trial. Clin Rehabil 2018;32:1328-39.
8. Félix E, Gimenes AC, Costa-Carvalho BT. Effects of inspiratory muscle training on lung volumes, respiratory muscle strength, and quality of life in patients with ataxia telangiectasia. Pediatr Pulmonol 2014;49:238-44.
9. Vainshelboim B. Exercise training in idiopathic pulmonary fibrosis: is it of benefit? Breathe (Sheff) 2016;12:130-8.
10. Swigris JJ, Kuschner WG, Jacobs SS, Wilson SR, Gould MK. Health-related quality of life in patients with idiopathic pulmonary fibrosis: a systematic review. Thorax 2005;60:588-94.
11. American Thoracic Society/European Respiratory S. ATS/ERS Statement on respiratory muscle testing. Am J Respir Crit Care Med 2002;166:518-624.
12. Wen AS, Woo MS, Keens TG. How many maneuvers are required to measure maximal inspiratory pressure accurately. Chest 1997; 111:802-7.
13. ATS/ERS Statement on respiratory muscle testing. Am J Respir Crit Care Med 2002;166:518-624.
14. Miller MR, Crapo R, Hankinson J, et al. General considerations for lung function testing. Eur Respir J 2005;26:153-61.
15. Brooks D, Solway S, Gibbons WJ. ATS statement on six-minute walk test. Am J Respir Crit Care Med 2003;167:1287.
16. Holland AE, Spruit MA, Troosters T, et al. An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. Eur Respir J 2014;44:1428-46.
17. Enright PL, Sherrill DL. Reference equations for the six-minute walk in healthy adults. Am J Respir Crit Care Med 1998;158:1384-7.
18. Bozkurt B BA, Saryal S, Uzun Ö, Tulumoğlu , Akkoca Ö. Translation and validation of the Turkish version of the St. George's Respiratory Questionnaire in patients with chronic obstructive pulmonary disease. Tuberk Toraks 2012;60:138-47.
19. Craig CL, Marshall AL, Sjostrom M, et al. International physical activity questionnaire: 12-country reliability and validity. Med Sci Sports Exerc 2003;35:1381-95.
20. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. Arch Neurol 1989;46:1121-3.
21. Pietro KM, Ricardo G, Rui G, et al. Relationship of pectoralis muscle area and skeletal muscle strength with exercise tolerance and dyspnea in interstitial lung disease. Sarcoidosis Vasc Diffuse Lung Dis 2017;34:200-8.
22. Algina J, Olejnik S. Sample Size Tables for Correlation Analysis with Applications in Partial Correlation and Multiple Regression Analysis. Multivariate Behav Res 2003;38:309-23.
23. Casas JP, Abbona H, Robles A, López AM. [Normal lung volumes in patients with idiopathic pulmonary fibrosis and emphysema]. Medicina (B Aires) 2008;68:282-4.
24. Naranjo-Orellana J, Santalla A. Long-Term Combined Training in Idiopathic Pulmonary Fibrosis: A Case Study. Int J Environ Res Public Health 2020;17.
25. Durdu H, Yurdalan SU, Ozmen I. Clinical significance of pectoralis muscle strength in elderly patients with idiopathic pulmonary fibrosis. Sarcoidosis Vasc Diffuse Lung Dis 2022;39:e2022009.
26. Case AH, Hellkamp AS, Neely ML, et al. Associations between Patient-reported Outcomes and Death or Lung Transplant in

Idiopathic Pulmonary Fibrosis. Data from the Idiopathic Pulmonary Fibrosis Prospective Outcomes Registry. Ann Am Thorac Soc 2020;17:699-705.
27. Vainshelboim B, Oliveira J, Fox BD, Kramer MR. The Prognostic Role of Ventilatory Inefficiency and Exercise Capacity in Idiopathic Pulmonary Fibrosis. Respir Care 2016;61:1100-9.
28. Singer J YE, Katz PP, Sanchez G, Iribarren C, Eisner MD, Blanc PD. Respiratory and skeletal muscle strength in chronic obstructive pulmonary disease: impact on exercise capacity and lower extremity function J Cardiopulm Rehabil Prev 2011;31:111-9.
29. Kim SH, Shin MJ, Shin YB, Kim KU. Sarcopenia Associated with Chronic Obstructive Pulmonary Disease. J Bone Metab 2019;26:65-74.
30. Faverio P, Fumagalli A, Conti S, et al. Sarcopenia in idiopathic pulmonary fibrosis: a prospective study exploring prevalence, associated factors and diagnostic approach. Respir Res 2022;23:228.
31. Cremers JP, Drent M, Elfferich MD, et al. Body composition profiling in a Dutch sarcoidosis population. Sarcoidosis Vasc Diffuse Lung Dis 2013;30:289-99.
32. Antwi-Boasiako C, Kollie MF, Kyeremeh KA, et al. Associations between spirometric measures and exercise capacity in type 2 diabetes. Diabetes Metab Syndr 2023;17:102831.
33. Satia I, Farooqi MAM, Cusack R, et al. The contribution of FEV(1) and airflow limitation on the intensity of dyspnea and leg effort during exercise. Insights from a real-world cohort. Physiol Rep 2020;8:e14415.
34. Hsia CC. Cardiopulmonary limitations to exercise in restrictive lung disease. Med Sci Sports Exerc 1999;31:S28-32.
35. Moderno EV, Yamaguti WP, Schettino GP, et al. Effects of proportional assisted ventilation on exercise performance in idiopathic pulmonary fibrosis patients. Respir Med 2010;104:134-41.
36. Chiu KL, Hsieh PC, Wu CW, Tzeng IS, Wu YK, Lan CC. Exercise training increases respiratory muscle strength and exercise capacity in patients with chronic obstructive pulmonary disease and respiratory muscle weakness. Heart Lung 2020;49:556-63.
37. Morino A, Takahashi H, Chiba H, Ishiai S. Daily physical activity affects exercise capacity in patients with idiopathic pulmonary fibrosis. J Phys Ther Sci 2017;29:1323-8.
38. Wallaert B, Monge E, Le Rouzic O, Wémeau-Stervinou L, Salleron J, Grosbois JM. Physical activity in daily life of patients with fibrotic idiopathic interstitial pneumonia. Chest 2013;144:1652-8.
39. Singh SJ, Puhan MA, Andrianopoulos V, et al. An official systematic review of the European Respiratory Society/American Thoracic Society: measurement properties of field walking tests in chronic respiratory disease. Eur Respir J 2014;44:1447-78.
40. Warburton DER, Bredin SSD. Health benefits of physical activity: a systematic review of current systematic reviews. Curr Opin Cardiol 2017;32:541-56.
41. Kreuter M, Swigris J, Pittrow D, et al. The clinical course of idiopathic pulmonary fibrosis and its association to quality of life over time: longitudinal data from the INSIGHTS-IPF registry. Respir Res 2019;20:59.
42. Bourke SC, Tomlinson M, Williams TL, Bullock RE, Shaw PJ, Gibson GJ. Effects of non-invasive ventilation on survival and quality of life in patients with amyotrophic lateral sclerosis: a randomised controlled trial. The Lancet Neurol 2006;5:140-7.
43. Defi IR, Otafirda MV, Novitri N, Rachmi A. Feasibility of inspiratory muscle training as a rehabilitation program for chronic kidney disease patients in a developing country. Eur Rev Med Pharmacol Sci 2023;27:8330-9.
44. Silva VG, Amaral C, Monteiro MB, Nascimento DM, Boschetti JR. Effects of inspiratory muscle training in hemodialysis patients. J Bras Nefrol 2011;33:62-8.
45. Figueiredo PHS, Lima MMO, Costa HS, et al. Effects of the inspiratory muscle training and aerobic training on respiratory and functional parameters, inflammatory biomarkers, redox status and quality of life in hemodialysis patients: A randomized clinical trial. PLoS One 2018;13:e0200727.
46. Agrawal SR, Joshi R, Jain A. Correlation of severity of chronic obstructive pulmonary disease with health-related quality of life and six-minute walk test in a rural hospital of central India. Lung India 2015;32:233-40.
47. Arena R, Myers J, Williams MA, et al. Assessment of functional capacity in clinical and research settings: a scientific statement from the American Heart Association Committee on Exercise, Rehabilitation, and Prevention of the Council on Clinical Cardiology and the Council on Cardiovascular Nursing. Circulation 2007;116:329-43.
48. Rasekaba T, Lee AL, Naughton MT, Williams TJ, Holland AE. The six-minute walk test: a useful metric for the cardiopulmonary patient. Intern Med J 2009;39:495-501.
49. Li J, Xu X, Sun J, et al. Activities of daily living, life orientation, and health-related quality of life among older people in nursing homes: a national cross-sectional study in China. Qual Life Res 2020;29:2949-60.
50. Christiansen L, Sanmartin Berglund J. Health-related quality of life and related factors among a sample of older people with cognitive impairment. Nurs Open 2019;6:849-59.
51. Meilleur KG, Linton MM, Fontana J, et al. Comparison of sitting and supine forced vital capacity in collagen VI-related dystrophy and laminin alpha2-related dystrophy. Pediatr Pulmonol 2017;52:524-32.