

# Effects of comprehensive and intensive pulmonary rehabilitation and nutritional support on quality of life and functional status in patients with chronic obstructive pulmonary disease

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## Abstract

**Objective:** To investigate the effects of pulmonary rehabilitation (PR) and combined nutritional support therapy on quality of life (QoL) and functional status in patients with chronic obstructive pulmonary disease (COPD).

**Methods:** This pre-and post-intervention prospective exploratory study involved 64 patients with stable stage three to four COPD. Oral nutritional support and personalized diet were combined with an intense and comprehensive PR program. Baseline and 8-week follow-up scores were compared for the 6-minute walk test (6MWT), incremental shuttle walking test (ISWT), St. George's Respiratory Questionnaire (SGRQ), pulmonary function tests (PFT), P<sub>Imax</sub>-P<sub>E<sub>max</sub></sub>, arterial blood gas (ABG), respiratory rate (RR), handgrip strength, Borg and modified Medical Research Council dyspnoea scale scores and fat-free mass index.

**Results:** Significant improvements were found in functional status (6MWT: 86.72 m, ISWT: 76.24 m), QoL (SGRQ total: 13.86), PFT, ABG, RR, dyspnoea, upper extremity muscle strength and hand-body composition.

**Conclusion:** Nutritional support with comprehensive and intensive PR can significantly improve physical performance, QoL, dyspnoea and body composition in COPD. The improvement in QoL

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was greater than that reported in previous studies. Because two modalities were combined in this study, future randomized controlled studies are needed to confirm the extent and contribution of these modalities to the outcomes.

### Keywords

Pulmonary rehabilitation, nutritional support, body composition, exercise capacity, quality of life, chronic obstructive pulmonary disease, functional status, dyspnoea

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### Introduction

Chronic obstructive pulmonary disease (COPD) is a common, preventable and treatable disease characterized by persistent respiratory symptoms and airway limitation. COPD is a main cause of chronic morbidity and mortality worldwide. In 2012, more than three million people (6% of all deaths) died from COPD.<sup>1</sup> The prevalence of COPD is 6.9% in Turkey; 20% in females and 80% in males.<sup>2</sup> It has been estimated that the global burden of COPD will increase in the following decades owing to ongoing exposure to COPD risk factors and an aging population.<sup>3</sup> Clinical deterioration, especially in the advanced stages of the condition and its associated complications, reduces patient quality of life (QoL) and increases treatment costs. Therefore, cost effectiveness and long-term follow-up are important requirements in the treatment of COPD. Evidence-based contributions to pulmonary rehabilitation (PR) and nutritional support are becoming increasingly prominent. PR is a multidisciplinary program that aims to improve the physical and emotional status of patients with chronic respiratory disease and to establish lasting behaviours to improve health. PR should be considered part of patient management and should include a multidisciplinary team of health care professionals to conduct a thorough evaluation.<sup>4</sup> The optimum benefit is obtained from PR programs

that last 6 to 8 weeks,<sup>1</sup> and few studies have reported benefits from extending the program to 12 weeks or more. However, some post-2015 studies have reported substantial improvements from programs lasting 12 weeks or longer.<sup>5</sup> A supervised exercise training course that includes endurance training, intermittent training and resistance or strength training is recommended twice a week. Such rehabilitation programs should be individualized to maximize the scope and intensity of personal functional gains.<sup>1</sup> Rehabilitation is the most effective treatment strategy to improve dyspnoea, health status and exercise tolerance,<sup>6</sup> and PR is appropriate for most patients with COPD. Particularly for patients with moderate and severe COPD,<sup>7</sup> improvements have been observed in functional exercise capacity and health-related QoL. PR is also one of the most cost-effective treatment strategies; it costs an estimated £2,000 to £8,000 per year to improve QoL.<sup>8</sup> However, there are many obstacles to the full implementation of PR. Some patients lack awareness of the suitability or benefits of PR programs, sometimes because of the rehabilitation practitioner's lack of knowledge. These factors can limit program completion. Major obstacles to achieving full participation include geographical limitations, cultural differences, finance, transportation and logistics.<sup>9</sup> Body composition abnormalities are common in chronic lung diseases, and

nutritional support is often required. Malnutrition and cachexia are observed in 26% to 47% of patients with COPD.<sup>10</sup> In addition to systemic inflammation, many other factors, such as tissue hypoxia, increased resting energy consumption, use of corticosteroids, decreased protein synthesis, increased protein degradation, endocrinological pathologies and decreased dietary intake, cause weight loss.<sup>11</sup> Low body mass index (BMI) and especially low fat-free body mass in patients with COPD are associated with poor prognosis.<sup>12</sup> For COPD patients who have poor diets, nutritional supplementation can promote weight gain and substantially improve respiratory muscle strength and general health-related QoL.<sup>13</sup> Better survival after weight gain has been reported for severe COPD patients with BMI below 25.<sup>14</sup> Skeletal muscle weakness in individuals with COPD is characterized by decreased muscle strength and endurance and reduced muscle mass, especially in the lower extremities. Recent studies have indicated that upper extremity muscle strength is correlated with exercise capacity, QoL and dyspnoea.<sup>15</sup> Burtin et al.<sup>16</sup> showed that, in addition to such known predictors such as age, dyspnoea, airflow obstruction (ADO) index and BMI, the identification of handgrip weakness provides prognostic data and may play a role in the rapid multidimensional assessment of COPD patients; furthermore, handgrip strength (HGS) was strongly linked to mortality in this study. Another study found that a multidisciplinary PR program and oral nutritional support improved sense of dyspnoea, exercise capacity and QoL in COPD patients.<sup>17</sup> In addition, concurrent nutritional supplementation with PR is beneficial in the treatment of cachexia associated with increased mortality independent of COPD.<sup>11</sup> Many studies have investigated the benefits of PR and nutritional support in individuals with COPD, and most of these studies

have made significant contributions to medical science and treatment of COPD. However, COPD remains a common global public health challenge with a high prevalence of morbidity and mortality. Therefore, cost-effective treatment strategies with long-term efficacy are still required. One study of stable COPD patients that compared comprehensive PR with conventional PR found that comprehensive PR substantially improved exercise capacity and QoL.<sup>18</sup> Therefore, in the present study, we aimed to investigate whether, compared with previous studies, greater improvements in functional capacity and QoL could be achieved by creating a more comprehensive and more intensive PR program and a specialized dietary and nutritional support program for each patient. We adding wrist and finger exercises following evidence that reduced HGS can provide prognostic data for COPD patients and is strongly associated with mortality.<sup>16</sup> We also extended the evaluation criteria to include functional capacity, QoL, respiratory rate, pulmonary function tests, respiratory muscle strength (P<sub>Imax</sub>-P<sub>E<sub>max</sub></sub>), arterial blood gas (ABG), upper extremity muscle strength, dyspnoea perception assessments and body composition analysis.

## Subjects and methods

This was a pre- and post-intervention, prospective, single group exploratory study. Participants were outpatients with stable stage three to four COPD admitted to the PR unit of our Department of Chest Diseases between 2015 and 2018 who met the inclusion criteria.

### *Inclusion criteria*

The clinical diagnosis of COPD was based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD)

guideline.<sup>1</sup> COPD grades were assigned as per the GOLD classification according to the severity of airflow limitation, which was based on post-bronchodilator forced expiratory volume in 1s (FEV1). Patients exhibiting nutritional depletion and meeting at least one of the following criteria<sup>19</sup> were considered appropriate for inclusion: a) BMI (BM/height squared)  $<21 \text{ kg/m}^2$ , fat-free BMI (fat-free mass index [FFMI]: fat-free mass [FFM]/height squared)  $<15 \text{ kg/m}^2$  for women or  $16 \text{ kg/m}^2$  for men, or b) BMI  $<25 \text{ kg/m}^2$  plus weight loss of at least 5% over 1 month or at least 10% over 6 months before admission.

### Exclusion criteria

Patients with disabling conditions such as neuromuscular disorders, malignant disorders, unstable cardiovascular diseases, orthopaedic problems or severe pulmonary hypertension, and those unwilling to complete the program, were excluded. Patients were also excluded if they experienced acute exacerbation over the previous 4 weeks, lack of motivation or poor compliance, lack of support from their families during the study, transportation problems or if they did not volunteer to participate in the study.

Ethical approval was obtained from the ethics committee of Necmettin Erbakan University, Konya, Turkey (App. No.: 2014-664), and written informed consent was obtained from each participant. Before the PR program, pulmonary function tests (forced vital capacity [FVC], FVC%, FEV1, FEV1%, FEV/FVC, forced expiratory flow [FEF] 25 to 75, FEF 25% to 75%) were conducted. In addition, maximum inspiratory pressure (MIP or P<sub>I</sub>max) and maximum expiratory pressure (MEP or P<sub>E</sub>max) measurements, which are indirect indicators of respiratory muscle strength, were also performed using a MIP-MEP meter. ABG was measured using a blood gas measuring device (ABL

700, Radiometer Copenhagen, Denmark) in the intensive care unit of the chest diseases department. A HGS test is considered an objective measure of upper extremity performance,<sup>20</sup> and helps to determine treatment goals and evaluate treatment effectiveness.<sup>21</sup> Left and right HGS measurements were performed using a digital hand dynamometer (Jamar Plus, model number: 12-0604 Digital Dynamometer; Patterson Medical, Bolingbrook, IL, USA) to measure upper extremity muscle strength. Functional status was measured using the 6-minute walk test (6MWT) and incremental shuttle walking test (ISWT). QoL was measured using St. George's Respiratory Questionnaire (SGRQ);<sup>22</sup> lower scores indicate better QoL. Dyspnoea perception was assessed at rest using both the Borg<sup>23</sup> and modified Medical Research Council (mMRC) dyspnoea scales.<sup>24</sup> BMI, FFMI, FFM and fat mass were measured using a body composition analyser (Tanita BC-418 Segmental Body Composition Analyzer, Tanita Corp, Tokyo, Japan). Patients' medical histories, including concomitant diseases and current medications, were obtained. All the above evaluations were used to create an intensive and comprehensive PR program for each patient. Pulmonary function and P<sub>I</sub>max and P<sub>E</sub>max pulmonary function tests were performed by an experienced technician; body composition analyses were conducted by an expert dietician; field tests, upper extremity muscle strength measurement, QoL evaluation and dyspnoea evaluation were conducted by a PR nurse. The PR nurse also trained patients in the use of an inhaler device. The expert dietician instructed patients about the importance of nutritional support. Participants received one 2-hour PR session 3 days a week for 8 weeks. The PR program was tailored according to each participant's needs, and included exercise training (wrist and finger strengthening exercises, endurance training

for lower and upper extremity muscles, active strength training and stretching relaxation exercises), respiratory muscle exercises, bronchial cleansing techniques, coping methods for shortness of breath, and training of patients and their relatives (i.e. information about the nature and course of COPD, and the benefits of pulmonary rehabilitation). The duration of the intense and comprehensive exercise was between approximately 100 to 120 minutes per day in this study, which is longer than the typical exercise durations reported in previous studies (e.g. 45, 60, 80 minutes).<sup>8</sup> During this period, patients' general condition, pulse, blood pressure and oxygen saturation were closely monitored. Both endurance and strength exercises for the lower extremities were performed intermittently using patient-specific methods. The muscles targeted in upper extremity exercises were the pectoral, latissimus dorsi, deltoid, trapezius, bicep and tricep muscles. Different exercise methods were used at different times for each of these muscle groups. For example, two types of exercises were used for the pectoral muscles, three for the latissimus dorsi, three for the deltoids and two for the biceps. These exercises, and the additional wrist and finger exercises, increased the duration of the PR program. The program was designed to target 70% to 80% of the maximum capacity measured in the initial patient evaluation. As previous studies indicate that HGS is also affected in patients with COPD,<sup>16</sup> finger and wrist exercises were added as they could be useful in patients' daily life activities (Appendix 1). In previous studies using free weights and a weight training station, the loads were determined as 70% to 80% of the maximum load the patient could lift once;<sup>8</sup> the maximum capacity for the lower extremity endurance training was calculated according to ISWT measurements. To prevent weight loss and restore muscle atrophy, a body composition

analysis was initially performed for each patient, and a personalized diet determined by the expert dietician. In addition to the personalized diet, patients with an FFMI  $<16 \text{ kg/m}^2$  for men and  $<15 \text{ kg/m}^2$  for women received oral nutritional therapy. Oral nutritional support was given as a liquid package three times; each 125 ml package contained 300 kcal (2.4 kcal/mL), 18 g of protein (E24%), 11.75 g of fat (E35%) and 30.5 g of carbohydrate (E41%). All participants were assessed just before and after the end of the PR program and all measured parameters compared with each other.

### *Statistical analysis*

The data obtained were analysed using SPSS, version 23.0 statistics software (IBM Corp., Armonk, NY, USA). The conformity of the data to the normal distribution and the coefficient of variation were evaluated using *n* and histogram graphs. The *t*-test for paired samples was used to compare the data obtained before and after the PR program, as the data were normally distributed. A  $P < 0.05$  was accepted as significant in all analyses.

### **Results**

Of 100 outpatients admitted to the PR unit, 66 patients were able to complete the study (one patient had pulmonary thromboembolism, two had acute exacerbation and 31 did not complete the program owing to transportation and financial problems). Of the 66 patients, 64 were male and two female; the mean age ( $\pm$  standard deviation) was  $63.27 \pm 7.43$  years. The disease duration was  $6.63 \pm 5.99$  years, and mean smoking history was  $50.18 \pm 21.46$  pack-years. Twenty-six patients (39%) had additional diseases (Table 1). Regarding drugs used to treat COPD, 26 patients (54.5%) used a combination of long-acting

anticholinergics, long-acting beta-agonists, inhaled steroids and short-acting beta-agonists (Table 2).

Changes in exercise capacity and functional status are shown in Table 3. Significant increases were observed in 6MWT scores ( $P < 0.001$ ) and ISWT

scores ( $P < 0.001$ ). The SGRQ scores, which indicate changes in QoL, showed significant improvements in all parameters related to PR (SGRQ symptom score:  $P = 0.018$ ; SGRQ activity score:  $P < 0.001$ ; SGRQ impact score:  $P < 0.001$ ; and SGRQ total score:  $P < 0.001$ ) (Table 4). A comparison of pulmonary function before and after PR showed significant improvements in all parameters (FVC:  $P = 0.025$ ; FVC%:  $P = 0.032$ ; FEV1:  $P = 0.003$ ; FEV1%:  $P = 0.003$ ; and (FEF 25%–75%:  $P = 0.013$ ), except for FEV/FVC (Table 5). Changes in MIP (PI<sub>max</sub>) and MEP (PE<sub>max</sub>) were examined. The MIP results showed a significant change ( $P = 0.08$ ). However, the MEP changes were not significant (Table 6). A comparison of the ABG results before and after PR showed a significant improvement in the values of PaO<sub>2</sub> ( $P = 0.007$ ) and SaO<sub>2</sub> ( $P = 0.003$ ) (Table 7). There was a significant decrease in respiratory rate after PR ( $P = 0.002$ ), and a significant increase in upper extremity muscle strength (as measured by the digital hand dynamometer) after PR (right hand:  $P = 0.024$  and left hand:  $P = 0.003$ ) (Table 8). Regarding dyspnoea perception, significant improvements were observed after PR in both Borg ( $P = 0.017$ ) and mMRC scores ( $P = 0.011$ )

**Table 1.** Patient demographic and clinical characteristics.

Characteristics	Mean or proportion
Patients (n)	66
Year (year $\pm$ SD)	63.27 $\pm$ 7.43
Sex (male/female)	64/2
History of smoking (pack-year $\pm$ SD)	50.18 $\pm$ 21.46
History of COPD (year $\pm$ SD)	6.63 $\pm$ 5.99
Additional diseases (no/yes)	40/26 (39%)
Additional disease rates	HT: 16 (24.24%) ACD: 8 (12%) DM: 6 (9%) CHF: 2 (3%) LC: 2 (3%)

ACD: atherosclerotic cardiovascular disease; CHF: congestive heart failure; DM: diabetes mellitus; HT: hypertension; LC: lung cancer; SD: standard deviation; COPD: chronic obstructive pulmonary disease.

**Table 2.** Drugs used to treat COPD.

Drug groups	Frequency	Percentage
Short-acting anticholinergics and short-acting beta-agonists	2	3.0
Long-acting anticholinergics	2	3.0
Short-acting beta-agonists and long-acting anticholinergics	2	3.0
Long-acting anticholinergics and long-acting beta-agonists	4	6.1
Long-acting anticholinergics, long-acting beta-agonists and theophylline	6	9.1
Long-acting anticholinergics, long-acting beta-agonists, inhaled steroids and short-acting beta-agonists	36	54.5
Long-acting anticholinergics, long-acting beta-agonists, inhaled steroids, short-acting beta-agonists and theophylline	14	21.2

COPD: chronic obstructive pulmonary disease.

**Table 3.** Results for 6-minute walk test and incremental shuttle walking test.

Exercise capacity measurements	Before PR mean	After PR mean	Mean change	P
6MWT (m)	278.75 ± 153.16	365.48 ± 136.14	86.72	0.000
ISWT (m)	144.06 ± 124.57	220.30 ± 180.94	76.24	0.000

ISSWT: incremental shuttle walking test; PR: pulmonary rehabilitation; 6MWT: 6-minute walk test.

**Table 4.** Quality of life scores before and after pulmonary rehabilitation.

SGRQ	Before PR mean	After PR mean	Mean change	P
SGRQ symptom score	59.80 ± 18.66	53.04 ± 20.11	6.76	0.018
SGRQ activity score	75.47 ± 25.67	58.22 ± 30.05	17.25	0.000
SGRQ impact score	47.67 ± 23.76	33.45 ± 20.43	14.22	0.000
SGRQ total score	58.07 ± 21.40	44.21 ± 22.01	13.86	0.000

PR: pulmonary rehabilitation; SGRQ: St. George's Respiratory Questionnaire.

**Table 5.** Changes in pulmonary function after pulmonary rehabilitation.

PFTs	Before PR mean	After PR mean	Mean change	P
FVC (l)	2.071 ± 0.75	2.236 ± 0.78	0.164	0.025
FVC (%)	55.372 ± 17.70	59.742 ± 19.65	4.369	0.032
FEV1 (L)	1.299 ± 0.62	1.396 ± 0.65	0.097	0.003
FEV1 (%)	43.633 ± 20.62	47.715 ± 20.65	4.081	0.003
FEV1/FVC (%)	60.206 ± 15.36	61.078 ± 13.26	0.872	0.628
FEF 25–75 (L)	0.930 ± 0.66	1.030 ± 0.84	0.100	0.050
FEF 25–75 (%)	31.239 ± 20.41	34.584 ± 24.41	3.345	0.013

PFT: pulmonary function test; FEF 25–75: forced expiratory flow between 25% and 75% of FVC; FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity; PR: pulmonary rehabilitation.

**Table 6.** MIP (PImax)-MEP (PEmax) changes after pulmonary rehabilitation.

MIP-MEP (PImax-PEmax)	Before PR mean	After PR mean	Mean change	P
MIP (PImax) (cm H <sub>2</sub> O)	48.45 ± 17.49	51.96 ± 15.71	3.51	0.083
MEP (PEmax) (cm H <sub>2</sub> O)	68.57 ± 24.54	71.72 ± 23.08	3.15	0.119

MEP (PEmax): maximal expiratory pressure; MIP (PImax): maximal inspiratory pressure; PR: pulmonary rehabilitation.

**Table 7.** Arterial blood gas changes after pulmonary rehabilitation.

ABG changes	Before PR mean	After PR mean	Mean change	P
pH	7.40 ± 0.05	7.42 ± 0.08	0.019	0.144
PaCO <sub>2</sub> (mmHg)	35.98 ± 4.20	34.53 ± 5.32	1.445	0.067
PaO <sub>2</sub> (mmHg)	62.39 ± 11.12	67.48 ± 9.24	5.096	0.007
HCO <sub>3</sub> (mEq/L)	22.48 ± 3.37	22.14 ± 3.60	0.334	0.489
SaO <sub>2</sub> (%)	90.44 ± 4.27	92.46 ± 3.68	2.021	0.003

ABG: arterial blood gas; HCO<sub>3</sub>: bicarbonate; PaCO<sub>2</sub>: partial pressure of carbon dioxide; pH: power + H; PaO<sub>2</sub>: partial pressure of oxygen; PR: pulmonary rehabilitation; SaO<sub>2</sub>: oxygen saturation in arterial blood.

**Table 8.** Changes in upper extremity muscle strength after pulmonary rehabilitation.

Hand grip strength	Before PR mean	After PR mean	Mean change	P
Right hand (kg)	33.75 ± 11.92	38.25 ± 14.43	4.50	0.024
Left hand (kg)	31.57 ± 10.51	36.96 ± 12.98	5.38	0.003

PR: pulmonary rehabilitation

**Table 9.** Changes in dyspnoea perception after pulmonary rehabilitation.

Dyspnoea perception scale	Before PR mean	After PR mean	Mean change	P
BORG	2.21 ± 1.08	1.75 ± 1.00	0.46	0.017
mMRC	2.66 ± 1.10	2.21 ± 1.26	0.45	0.011

BORG: Borg dyspnoea scale; mMRC: modified Medical Research Council dyspnoea scale; PR: pulmonary rehabilitation.

**Table 10.** Changes obtained with pulmonary rehabilitation and dietary support.

Body composition analysis	Before PR mean	After PR mean	Mean change	P
BMI	25.20 ± 1.00	25.37 ± 0.93	0.17	0.463
FFMI	18.91 ± 0.51	19.79 ± 0.49	0.88	0.002
FFM (kg)	53.99 ± 1.59	56.55 ± 1.60	2.56	0.002
FM (kg)	18.50 ± 1.72	16.24 ± 1.53	2.26	0.002

BMI: body mass index; FM: fat mass; FFM: fat-free mass; FFMI: fat-free mass index; PR: pulmonary rehabilitation.

(Table 9). There were 16 male patients with FFMI <16 kg/m<sup>2</sup> and 1 female patient with FFMI <15 kg/m<sup>2</sup>, so oral nutritional therapy was added to these patients' diets. There was a significant increase in FFMI ( $P=0.002$ ) and FFM ( $P=0.002$ ). A significant reduction in fat mass ( $P=0.002$ ) was achieved through PR combined with

personalized dietary and nutritional support therapies (Table 10).

## Discussion

Our results indicate that the addition of a personalized dietary supplement (dietary



program and oral nutrition solutions) developed by an expert dietician as part of a comprehensive and intensive PR program produced improvements. This was a comprehensive examination of changes in nine parameters, and significant improvements were achieved in almost all parameters. There were significant improvements in functional status (6MWT: 86.72 m, ISWT: 76.24 m), QoL, pulmonary function tests, ABG, respiratory rate, sense of dyspnoea, upper extremity muscle strength and body composition. Of these, the most important improvements were in ISWT and 6MWT scores, as indicators of exercise capacity and physical performance, and SGRQ scores. These results are among the highest gains reported in the literature. A Cochrane Database systematic review that evaluated PR in patients with COPD reported the following findings: 38 studies involving 1879 patients were examined for significant changes in 6MWT, and increases above 43.93 m were considered significant; ISWT was evaluated in 8 studies with 694 patients, and increases of more than 39.77 m were considered significant; SGRQ was evaluated in 19 studies with 1146 patients, and decreases of more than 6.89 were considered significant.<sup>6</sup> Another recent review found high-quality evidence for the effects of PR: a significant increase was observed in physical performance (6MWT distance: +44 m) and QoL (SGRQ: 6.9 points).<sup>25</sup> In the present study, the benefits gained by patients were higher than reported in previous studies.

In a meta-analysis that included 32 randomized controlled trials and that evaluated the addition of inspiratory muscle training to a general exercise training program in patients with COPD, a significant improvement was found for inspiratory muscle strength and endurance, functional exercise capacity, dyspnoea (Borg score) and QoL (Chronic Respiratory Disease Questionnaire).<sup>26</sup> In the present study, an

increase was found in P<sub>I</sub>max and P<sub>E</sub>max, but these changes were not significant. Significant improvements were also found for dyspnoea scores. Schroff et al. reported the greatest benefit in patients with the worst dyspnoea and exercise capacity scores, and reported a greater improvement than the clinically significant minimum difference in all patients. In the same study, patients participating in a hospital-based PR program and who had the lowest 6MWT scores experienced the greatest benefit in exercise capacity. The authors concluded that patients with COPD experienced a significant improvement in QoL, dyspnoea score, exercise capacity and depression, regardless of baseline pulmonary function, dyspnoea and exercise capacity.<sup>27</sup> Here, we examined patients with stage 3–4 COPD and observed significant improvements in pulmonary function, ABG values, dyspnoea scores, exercise capacity and QoL. A 4-unit drop in SGRQ total score after treatment is considered a minimal clinically significant change.<sup>28</sup> In the present study, QoL demonstrated significant improvements in all parameters and significant decreases in scores of SGRQ symptoms, activity, impact<sup>26</sup> and total score (13.86) after PR. Sciriha et al.<sup>29</sup> evaluated COPD patients with both the SGRQ questionnaire and the COPD assessment test (CAT). The findings showed that both QoL and CAT scores decreased significantly after PR, especially for patients with mMRC scores of 3 to 4. A subgroup analysis carried out as part of a meta-analysis evaluating PR in patients with COPD exacerbations found that the effects of PR depend on PR quality, and higher quality rehabilitation produces better results.<sup>30</sup> Eight studies were evaluated in this meta-analysis. The authors found that PR had significantly greater effects on SGRQ. There was high-quality evidence for an average increase in 6MWT scores and ISWT scores.<sup>30</sup> The comprehensive and

intensive PR program implemented in the present study produced better results than those reported in this meta-analysis. In a prospective cohort study by Ragaselvi et al.,<sup>31</sup> a significant improvement was demonstrated in the primary outcome parameters of 6-minute walk distance (6MWD) and SGRQ scores and SGRQ total score, indicating a strong correlation between change in 6MWD and change in SGRQ scores. Our study showed that nutritional supplementation with comprehensive and intensive PR produced significant improvements in all SGRQ parameters, and that this improvement was higher than most of the reported improvements in the literature. There were also significant improvements in 6MWT and ISWT scores. Previous studies on patients undergoing PR report no data indicating an increase in FEV1, and two studies have reported a smaller reduction in mean FEV1 in patients undergoing PR compared with those receiving only medication.<sup>32,33</sup> In the FIRST study (FEV1 as an Index of Rehabilitation Success Over Time), FEV1 changes in 190 patients undergoing PR were compared with changes in 67 patients receiving drug treatment alone. In the PR group, FEV1 increased from 1240 mL (57.3%) to 1252.4 mL (60.8%) after 3 years, whereas the values were 1367 mL (55%) at baseline and 1150 mL (51%) after 3 years in the controls, a significant difference.<sup>34</sup> Recently, these positive results have been confirmed in a retrospective study of 554 patients with very severe COPD; FEV1 values increased from  $970 \pm 260$  mL to  $1080 \pm 330$  mL after a 3-week PR.<sup>35</sup> Similar changes were observed in the present study and these increases were significant. These results suggest that lung functions recover in COPD patients undergoing PR, and the extent of the improvements can be considered to indicate the clinical success of the treatment. Previous studies have reported differing effects of PR on the results of ABG

analyses. Whereas some studies have detected no changes in ABG after PR,<sup>36,37</sup> others have reported significant improvements in PaO<sub>2</sub> and SaO<sub>2</sub> levels.<sup>38</sup> One study evaluating the efficacy of PR according to disease stage showed that PaO<sub>2</sub> level significantly increased in patients with severe and very severe COPD.<sup>39</sup> However, another study found that PaO<sub>2</sub> and SaO<sub>2</sub> significantly increased in normocapnic and hypercapnic patients with COPD receiving PR; the hypercapnic group showed a higher SaO<sub>2</sub> increase and a significant reduction in PaCO<sub>2</sub>.<sup>7</sup> In the present study, PaO<sub>2</sub>, SaO<sub>2</sub> and PaCO<sub>2</sub> values improved after PR, and the improvement was significant for PaO<sub>2</sub> and SaO<sub>2</sub>. In a study examining the effects of PR on exercise performance and physiological responses in patients with severe COPD, SaO<sub>2</sub> increased, whereas carbon dioxide production (VCO<sub>2</sub>) and respiratory rate decreased, but these results were insignificant.<sup>40</sup> The present study showed a significant increase in the values of FEV1, FVC, FEF 25 to 75, PaO<sub>2</sub> and SaO<sub>2</sub> and a significant decrease in respiratory rate after PR. The number of studies conducted on the effects of upper extremity training in patients with COPD undergoing PR is increasing. HGS is measured using a hydraulic hand dynamometer, which measures the muscle strength of the hands and distal upper extremity muscles. The muscle strength of the proximal upper extremities and shoulders can be measured using the one repetition maximum test. In a recent study using these two procedures, a significant correlation was found between upper extremity muscle strength, exercise capacity, QoL and feelings of dyspnoea.<sup>14</sup> Wang et al.<sup>41</sup> state that normal HGS values (varying according to age) are 28.1 to 49.7 kg (dominant hand) and 27.1 to 46.5 kg (non-dominant hand) for males, and 19.6 to 29.6 kg (dominant hand) and 18.7 to 28.9 kg (non-dominant hand) for females.

In the present study, a significant improvement was observed in exercise capacity, QoL, dyspnoea and grip strength after PR. Loss of FFM in patients with COPD is a poor prognostic parameter.<sup>42</sup> Individual nutritional therapy is an effective intervention for COPD, especially when combined with physical exercise for malnourished patients.<sup>42</sup> In a study investigating the effect of body composition on PR outcomes in patients with COPD, a significant increase was observed in exercise tolerance (6MWT: +40.62 m) and QoL, regardless of muscle weakness or total body weight.<sup>43</sup> In a study by Gurgun et al.,<sup>11</sup> patients received three packages of 250 mL nutritional fluid consisting of 53.3% energy from carbohydrate, 30% energy from fat and 16.7% energy from protein per day, and were also encouraged to continue to consume their usual meal portions. In our study, to prevent weight loss and restore muscle atrophy, baseline body composition analyses were performed, and a personalized diet determined by an expert dietician. In addition, oral nutritional therapy was added to the diet of patients' with lean BMI. Additionally, our exercise program was more intense. In the Gurgun et al. study, the exercise duration was 60 to 80 minutes compared with about 100 to 120 minutes in our study. Gurgun et al.<sup>11</sup> reported that in the group undergoing combined PR and nutritional support, FFMI was  $13.9 \pm 2.3$  to  $14.5 \pm 2.4$ , ( $P=0.001$ ) and SGRQ scores were as follows: symptom score (15.4), activity score (14), impact score (5.87) and total score (8.4). In the present study, body composition was significantly improved. We found a significant increase in FFMI and FFM, and a significant decrease in fat mass. SGRQ scores were higher than those reported in the study by Gurgun et al: activity score (17.25), impact score (14.22) and SGRQ total score (13.86).

## Limitations

One of the most important limitations of our study is the absence of a control group. We compared data before and after the program, in addition to comparing our findings with previous findings; however, the lack of a control group reduces the methodological quality of the study. A second limitation is that 31% of patients could not complete the study owing to transportation and financial problems. Another limitation was the unbalanced ratio between male and female participants. The prevalence of COPD is 6.9% in Turkey (20% in women and 80% in men). The number of expected female patients in the study was 16; however, only two of the 66 participants were female. It is not clear whether this factor affected the results. The sex ratio in the present study is similar to that in the study by Gurgun et al. (2 females and 44 males),<sup>11</sup> which is considered a valuable study in Turkey.

## Conclusion

The findings show that individual nutritional therapy and support combined with an intensive and comprehensive PR program produced significant improvements, especially in QoL (SGRQ) and functional status (6MWT, ISWT), in patients with COPD. This was a comprehensive study examining changes in nine different parameters, and significant improvements were found in almost all parameters. Significant improvements were also found in pulmonary function tests, ABG, respiratory rate, upper extremity muscle strength, dyspnoea scores (mMRC, Borg) and body composition. Our findings suggest that nutritional support combined with comprehensive and intensive PR can produce substantial improvements in physical performance, QoL, dyspnoea and body composition in patients with COPD. The most important finding is that

nutritional support combined with comprehensive and intensive PR produced significant improvements in all the SGRQ parameters, and this improvement is one of the highest reported in the literature. As this study uniquely combined two different modalities, it is unclear which modality had a greater effect on the results; therefore, future randomized controlled studies are needed to confirm the extent and contribution of these features to the outcomes. These results suggest that personalized diet, nutritional support and extensive and comprehensive PR are necessary components of the treatment of patients with COPD.

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### Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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## Appendix

### Appendix: Sample pulmonary rehabilitation program

Name-Surname:

	Type of exercise	Repetition number or time	Perform
1	Exercise bike (lower extremity endurance exercise)	15–30 minutes	X
2	Treadmill (lower extremity endurance exercise)	15–30 minutes	
3	Hand ergometer (upper extremity endurance training)	15 minutes	X
4	Stretching and relaxation exercises	5 minutes	
5	Weight station chest press exercise (for pectoral muscles)	3 × 8 repeats	X
6	Weight station chest butterfly movement (for pectoral muscles)	3 × 8 repeats	
7	Weight station wings movement from top to back (for latissimus dorsi muscles)	3 × 8 repeats	X
8	Weight station back and wing movement front to rear traction (for latissimus dorsi and paravertebral muscles)	3 × 8 repeats	X
9	Weight station back movement sitting on exercise mat front-to-back traction (for latissimus dorsi and paravertebral muscles)	3 × 8 repeats	X

(continued)

Continued.

	Type of exercise	Repetition number or time	Perform
10	Shoulder press with dumbbell (for deltoid muscles) (In dumbbell exercises, the weight that can be lifted by the patient 15 times is chosen. When the patient completes three sets without forcing, the weight is increased by 0.5 kg)	3 × 8 repeats	X
11	Side opening of the shoulder with dumbbell (for lateral part of deltoid muscles)	3 × 8 repeats	X
12	Front shoulder exercise with dumbbell (for front part of deltoid muscles)	3 × 8 repeats	
13	Biceps muscle exercise with dumbbell	3 × 8 repeats	X
14	Half-biceps muscle exercise with dumbbell (hammer movement)	3 × 8 repeats	X
15	Triceps muscle exercise at weight station	3 × 8 repeats	X
16	Stepping on exercise ladder (lower extremity strength exercise)	5 minutes	X
17	Sitting on a chair and standing up (lower extremity strength training)	5 minutes	
18	Quadriceps muscle extension with free weight (lower extremity strength training)	3 × 8 repeats	X
19	Quadriceps muscle extension in the centre of gravity (lower extremity strength exercise)	3 × 8 repeats	
20	Inspiratory/respiratory muscle exercise with threshold inspiratory muscle training	3–5 minutes	X
21	Inspiratory/expiratory muscle training with Triflo (huffing manoeuvre is performed 2 to 3 times after 20 repetitions)	2–3 minutes	
22	Respiratory muscle exercise with pursed lips breathing (The patient can also perform the pursed lips exercise while walking: inhale for 2 steps and exhale for 4 steps)	2–3 minutes	X
23	Diaphragmatic breathing exercise	2–3 minutes	X
24	Respiratory muscle exercise with Acapella or PEP valve device (huffing manoeuvre is performed 2 to 3 times after 20 repetitions)	2–3 minutes	X
25	Difficult expiration with controlled cough manoeuvre (The patient leans forward in the sitting position, makes a deep inspiration, holds his/her breath for a few seconds and coughs 2–3 times. He/she repeats this procedure after a short interval)	5–10 times	X
26	Difficult expiration with huffing technique (The patient takes a deep breath and immediately flexes the abdominal muscles and exhales the air by making a 'ha, ha, ha' sound)	5–10 times	
27	Percussion technique to help cleanse the bronchial passages (A cup-shape is made with the hands, and the drainage region is hit 5 times for 1 to 5 minutes)	2–3 minutes	X
28	Wrist and forearm exercise at weight station	3 × 8 repeats	
29	Wrist exercise with dumbbell	3 × 8 repeats	X
30	Hand bow and silicone finger exercise	3 × 8 repeats	X