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RESEARCH ARTICLE

THE ROLE OF GENDER REGARDING THE OUTCOMES OF PULMONARY REHABILITATION IN PATIENTS WITH COPD: A RETROSPECTIVE STUDY

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ABSTRACT

Purpose: Our aim is to compare the pulmonary rehabilitation outcomes of male and female patients diagnosed with COPD.
Material and Methods: In this retrospective study outpatient PR program, consisting of 16 sessions, two times a week for two months was applied to the patients with COPD (41 males, 41 females). arterial blood gas (ABG) analyzes and pulmonary function tests (PFT), 6-minute walking test (6MWT), dyspnea scale (mMRC), health-related quality of life (QoL) questionnaire (SF-36), disease-specific health status (SGRQ) were applied to all participants before and after PR.
Results: There was no statistically significant differences between the two groups before PR in terms of age, BMI, PFT parameters, and ABG results. Cigarette consumption was higher in men($p=0.02$). Quality of life survey results (SGRQ, SF36), HAD anxiety, mMRC were similar in both groups before PR($p>0.05$ for all). After PR, both clinical and statistically significant improvements were detected in 6mWD in both groups ($p <0.001$ for both). There was a significant improvement in all SGRQ scores in both genders ($p<0.05$ for all). While significant improvement was observed in all parameters of SF36 in women, significant improvement was found in only some parameters of SF36 in male patients. While HAD anxiety and depression scores significantly improved in female patients after PR, only anxiety score in male patients improved ($p=0.004$, $p=0.002$, $p=0.021$).
Conclusion: This study showed that PR has had a positive effect on many outcome measures, regardless of gender. After PR; The walking distance and QoL scores increased, perception of dyspnea, anxiety and depression score decreased in women with COPD.

Keywords: COPD, pulmonary rehabilitation, gender

INTRODUCTION

COPD is a disease with high mortality and morbidity which is the fourth major cause of death in the World but is predicted to be the 3rd leading cause of mortality by 2020(1). COPD is traditionally known as a male disease therefore, the diagnosis of COPD is delayed in female COPD patients (2,3). COPD causes increasing rates of morbidity and mortality in women today (3,4). It is known that the risk of developing COPD, disease progression and possible consequences of the disease can vary with gender (5,6). However, COPD disease does not receive the necessary attention within 'women's health problems'. There are not enough studies investigating

the effect of gender on both pharmacological and nonpharmacological treatment success.

Pulmonary rehabilitation (PR) is a comprehensive, interdisciplinary treatment approach that aims to improve the physical and emotional states of patients with COPD and to provide permanent health-promoting behaviors, including individually determined exercises such as exercise training, training and behavior change (1). A growing body of evidence highlights the importance of PR gains in patients with COPD (1). However, there are not enough studies comparing the outcomes of PR program in female COPD patients (7). Therefore, with this study, our aim is to compare the gender differences for the pulmonary rehabilitation outcomes of COPD patients who completed the outpatient PR program.

MATERIAL AND METHODS

Patients Selection

Ethics Committee approval for the study was obtained from the Dr. Suat Seren Chest Diseases and Thoracic Surgery Training and Research Hospital (49109414-806. 02/02/2017). This retrospective cross-sectional study is conducted in our hospital's outpatient pulmonary rehabilitation center during January 2012 and December 2016. During this time period 549 patients referred to our outpatient pulmonary rehabilitation program. All participants were stable patients with COPD (not any increase in the use of rescue medication, not worsening of pulmonary symptoms, and no ER admissions or unscheduled visits because of COPD worsening for the last four weeks,), who were diagnosed based on the definition of Global Initiative for Chronic Obstructive Lung Disease (GOLD) report (1).

Study Design and Assessment of Sociodemographic Data

The pulmonary rehabilitation program was set up at our hospital, which functions both as an education, research hospital and a general hospital. Our 8-week outpatient PR program has previously been described in detail (8,9). During this time period 41 female patients with COPD successfully completed the PR program. To obtain the control group which consists of male COPD patients was matched 1 to 1 with similar distributions of observed covariates. A total of 82 COPD patients, 41 male and 41 females, who were referred to the PR unit, were included in the study. The outpatient PR program, consisting of a total of 16 sessions, was performed twice a week for two months to all participants. According to our PR program, baseline demographic and severity data were recorded.

Pulmonary Function Tests and Quality of Life Questionaries

Before and after pulmonary rehabilitation 6-minute Walking Test (6MWT) and the pulmonary functional status of the patients were measured. All participants before and after PR; arterial blood gas (ABG) analysis and pulmonary function tests (PFT), 6-minute walking test (6MWT), dyspnea scale (mMRC), health-related quality of life questionnaire (SF-36), disease-specific quality of life (SGRQ) Hospital Anxiety and Depression Scale (HAD) were applied (10-14). Also, emergency admissions and hospital admissions in the last year were questioned before the OPR program. Dyspnea perceptions and health status were evaluated by mMRC and SF-36 scale and St. George Respiratory Questionnaire (SGRQ). 6mWD was performed to determine exercise capacities and predicted values of 6MWD is calculated for both gender for decreasing the gender differences in exercise capacity (15).

Statistical Analysis

SPSS 20.0 (IBM) program was used for statistical analyses. For the normality of the data Shapiro-Wilk test was used. For descriptive statistics median (interquartile range) or percentage were used where appropriate. Change (Δ) between post-intervention and baseline values were reported. Fisher's exact test were used for frequencies. For comparing baseline characteristics and Δ values medians Mann Whitney U test were used. Wilcoxon test was used to compare variables post-intervention and baseline in each group. A p value of <0.05 was considered statistically significant. When we calculated the power of this study with a 2-tailed test at the 0.05 level and with a sample size of 41 in both groups in order to find a difference of 40 meters in 6MWD (assuming a SD of 15 meters), the power was 86%.

RESULTS

The median age of the male and female participants was 63 (61/66), 60 (54/67) respectively (p=0.09). No statistically significant difference was found between two groups regarding age, pulmonary function test parameters, body mass index, number of emergency

Table 1. The demographic characteristics of the participants before pulmonary rehabilitation program

Variables	All Patients (n=82)	Male Patients (n=41)	Female Patients (n=41)	p*
Age (year)	63 (57/66)	63 (61/66)	60 (54/67)	0.099
BMI (kg/m^2)	26 (23/29)	27 (23/29)	26 (23/31)	0.536
Emergency admission (n/last year)	1 (0/3)	0 (0/3)	1 (0/3)	0.350
Hospitalization (n/last year)	0 (0/1)	0 (0/1)	0 (0/1)	0.863
Smoking History n(%)				
Smoker	7 (8,5)	3 (7,3)	4 (9,8)	
Ex-smoker	15 (18,3)	35 (85,4)	25 (61,0)	**0.027**
Never smoked	60 (73,2)	3 (7,3)	12 (29,3)	
Smoking (Packyears)	48 (25/76)	60 (38/80)	40 (30/62)	**0.002**
Devices n(%)				
Nebulizer	9 (11,1)	3 (7,3)	6 (14,6)	0.482
LTOT	8 (9,9)	1 (2,4)	7 (17,1)	0.057
NIMV	1 (1,2)	1 (2,4)	-	0.494
Pulmonary Function Test				
FEV1 (%)	46 (38/60)	46 (41/58)	45 (34/66)	0.759
FEV1/FVC	63 (56/72)	62 (56/68)	65 (56/78)	0.391
TLCO (%)	42 (26/53)	44 (28/56)	35 (24/51)	0.208
Blood Gase Analysis				
PaO_2 (mmHg)	75 (66/83)	75 (66/80)	75 (68/85)	0.490
$PaCO_2$ (mmHg)	39 (37/42)	40 (37/42)	39 (37/44)	0.833
$SatO_2$ (%)	95 (93/97)	95 (93/96)	96 (93/97)	0.338
6MWD (meter)	390 (318/430)	410 (335/455)	360 (280/415)	**0.013**
6 MWD predicted (%)	73 (58/83)	72 (59/82)	73 (58/83)	0.945
mMRC (1-5)	3 (2/4)	3 (2/4)	3 (3/4)	0.285
SGRQ (0-100)				
Symptom	46 (35/66)	46 (35/67)	46 (35/62)	0.771
Activity	67 (49/80)	61 (49/80)	73 (54/80)	0.188
Impact	40 (28/56)	37 (28/53)	41 (28/59) 52	0.758
Total	49 (37/62)	46 (36/62)	(40/62)	0.603
SF-36(0-100)				
Physical Function	55 (35/75)	60 (35/75)	50 (35/75)	0.515
Social Function	63 (50/88)	75 (63/88)	63 (38/75)	0.163
Physical Role	0 (0/56)	0 (0/50)	0 (0/75)	0.986
Emotional Role	33 (0/100)	33 (0/100)	0 (0/100)	0.095
General	45 (25/62)	45 (25/67)	40 (25/55)	0.398
Mental	64 (52/76)	68 (56/80)	64 (52/72)	**0.032**
Pain	62 (41/90)	72 (42/100)	58 (32/84)	0.154
Vitality	52 (35/70)	55 (45/75)	50 (30/65)	0.053
HAD (0-21)				
Anxiety	7 (5/11)	6 (4/9)	8 (5/11)	0.102
Depression	6 (3/9)	5 (2/7)	7 (5/10)	**0.016**

*Mann Whitney U Test or Chi Square Test, Data are expressed as median (interquartile range)
BMI: Body mass index, FEV1%: Forced expiratory volume in first second, FVC: Forced vital capacity, PaO2: partial oxygen pressure, PaCO2: Partial carbondioxide pressure, 6mWD:6 minute walk distance, SGRQ: St George Respiratory Questionnaire, SF-36: Short Form 36 Health Survey, HAD:Hospital Anxiety And Depression Scale, mMRC: Modified Research Council Dyspnea Scale, LTOT:Long Term Oxygen Treatment, NIMV: Non Invazıv Mechanical Ventilation

admissions and hospitalizations, arterial blood gas analysis results before pulmonary rehabilitation ($p<0.05$ for all) (Table 1). Smoking history and the amount of smoking was significantly higher in males

Table 2. The comparison of the parameters in both gender before and after pulmonary rehabilitation

Variables	Male (n=41)			Female (n=41)		p*
	Pre-PR	Post-PR	P*	Pre-PR	Post-PR	
Pulmonary Function Test						
FEV1 (%)	46(41/58)	51(41/61)	0.194	45(34/66)	53(33/68)	0.355
FEV1/FVC	62(56/68)	61(57/74)	0.695	65(56/78)	67(57/77)	0.861
TLCO (%)	44(28/56)	47(30/57)	0.155	35(24/51)	41(27/54)	0.188
Blood Gase Analysis						
PaO_2 (mmHg)	75(66/80)	80(73/87)	**<0.001**	75(68/85)	80(72/89)	**0.003**
$PaCO_2$ (mmHg)	40(37/42)	40(37/42)	0.327	39(37/44)	39(36/44)	0.414
$SatO_2$ (%)	95(93/96)	95(95/96)	0.094	96(93/97)	96 (95;97)	**0.044**
6MWD (meter)	410(335/455)	455(410/508)	**<0.001**	360(280/415)	415(311/460)	**<0.001**
6 MWD predicted (%)	72(59/82)	79(72/90)	**<0.001**	73(58/83)	81(67/92)	**<0.001**
mMRC (1-5)	3(2/4)	2(2/3)	**<0.001**	3(3/4)	2(1;3)	**<0.001**
SGRQ (0-100)						
Symptom	46(35/67)	41(30/57)	**0.014**	46(35/62)	38(25/52)	**0.002**
Activity	61(49/80)	55(42/66)	**0.002**	73(54/80)	59(38/73)	**<0.001**
Impact	37(28/53)	32(20/47)	**0.015**	41(28/59)	30(18/48)	**<0.001**
Total	46(36/62)	37(28/53)	**<0.001**	52(40/62)	41(28/52)	**<0.001**
SF-36(0-100)						
Physical Function	60(35/75)	65(45/80)	**0.016**	50(35/75)	70(50/80)	**<0.001**
Social Function	75(63/88)	88(63/100)	0.113	63(38/75)	75(63/100)	**0.006**
Physical Role	0(0/50)	50(0/100)	**0.017**	0(0/75)	75(25/100)	**0.001**
Emotional Role	33(0/100)	67(33/100)	0.578	0(0/100)	67(33/100)	**0.002**
General	45(25/67)	52(30/67)	0.626	40(25/55)	52(34/78)	**0.036**
Mental	68(56/80)	76(68/88)	**0.028**	64(52/72)	72(52/81)	**0.011**
Pain	72(42/100)	90(62/100)	**0.009**	58(32/84)	79(56/90)	**<0.001**
Vitality	55(45/75)	65(50/80)	**0.034**	50(30/65)	65(50/76)	**<0.001**
HAD (0-21)						
Anxiety	6 (4/9)	5(3/7)	**0.021**	8(5/11)	6(3/10)	**0.004**
Depression	5 (2/7)	5(2/7)	0.993	7(5/10)	5(2/8)	**0.002**

*Willcoxon Test. Data are expressed as median (interquartile range)

FEV1%: Forced expiratory volume in first second, FVC: Forced vital capacity, PaO2: partial oxygen pressure, PaCO2: Partial carbondioxide pressure, 6mWD:6 minute walk distance, SGRQ: St George Respiratory Questionnaire, HAD:Hospital Anxiety And Depression Scale, mMRC: Modified Research Council Dyspnea Scale

compared to females (p=0.02, p=0.002, respectively). The scores of general health status (SGRQ, SF36, HAD) and dyspnea scores (mMRC) were similar between two groups (Table 1). Only one parameter (mental health) of SF36 was statistically significant between two groups before PR (p=0.032) the other 7 parameters of SF36 (vitality, general health perceptions, physical functioning, emotional role functioning, physical role functioning, social role functioning, bodily pain) were similar between two groups (p=0.053, p=0.5, p=0.3, p=0.9, p=0.09, p=0.1, p=0.1 respectively). Women with COPD had higher HAD depression scores compared to male patients (Table 1).

After PR when we compare the outcomes; the pulmonary function test results including FEV1%, FEV1/FVC%, TLCO were not statistically different after PR in both groups (all p<0.05) (Table 2). PaO2 levels improved in both genders significantly after PR (p<0.001 for male p=0.003 for female). Saturation of oxygen was statistically improved (not clinically important) after PR in female participants however this gain in blood gas analysis was not seen in male group (p=0.04, p=0.09). 6mWD was significantly improved in both groups after PR (male p<0.0001, female p<0.001), this gain was also higher than minimal clinically important difference in both groups (Table 2). The gender corrected predicted 6mWD values were also significantly improved after PR in both gender (p<0.001 both). All parameters of SGRQ score were improved in both groups significantly (Table 2), also all parameters of SF36 were

Table 3. Comparison of changes in outcomes in two groups

Variables	Male Patients (n=41)	Female Patients (n=41)	p*
Pulmonary Function Test			
ΔFEV1 (%)	1 (-4/6)	1 (-4/7)	0.795
ΔFEV1/FVC	1 (-7/7)	0 (-6/7)	0.940
ΔTLCO (%)	1 (0/7)	1 (-3/12)	0.995
Blood Gase Analysis			
ΔPaO_2 (mmHg)	5 (0/13)	4 (-2/9)	0.318
Δ$PaCO_2$ (mmHg)	0 (-2/2)	0 (-4/3)	0.992
Δ$SatO_2$ (%)	1 (0/2)	0 (0/2)	0.830
Δ6MWD (meter)	40 (20/80)	40 (20/68)	0.775
6 MWD predicted (%)	7 (4/15)	8 (4/14)	0.758
ΔmMRC	-1 (-1/0)	-1 (-1/-1)	**0.036**
SGRQ(0-100)			
ΔSymptom	-5 (-20/1)	-9 (-19/-2)	0.321
ΔActivity	-7 (-13/0)	-11 (-26/0)	0.298
ΔImpact	-6 (-16/2)	-10 (-17/-2)	0.181
ΔTotal	-6 (-16/-2)	-9 (-18/-3)	0.268
SF-36(0-100)			
ΔPhysical Function	3 (0/20)	10 (0/25)	0.212
ΔSocial Function	0 (-13/25)	13 (0/25)	0.316
ΔPhysical Role	0 (0/50)	13 (0/50)	0.665
ΔEmotional Role	0 (-33/33)	33 (0/67)	**0.011**
ΔGeneral	0 (-10/15)	7 (-6/24)	0.218
ΔMental	4 (-4/20)	6 (-1/21)	0.833
ΔPain	0 (0/33)	14 (0/28)	0.226
ΔVitality	5 (-5/15)	15 (0/25)	0.081
HAD (0-21)			
ΔAnxiety	-1 (-4/1)	-2 (-3/0)	0.663
ΔDepression	0 (-2/2)	-1 (-5/0)	**0.029**

*Mann Whitney U Test. Data are expressed as median (interquartile range)
FEV1%: Forced expiratory volume in first second, FVC: Forced vital capacity, PaO_2: partial oxygen pressure, $PaCO_2$: Partial carbondioxide pressure, 6mWD:6 minute walk distance, SGRQ: St George Respiratory Questionnaire, SF-36: Short Form 36 Health Survey, HAD:Hospital Anxiety And Depression Scale, mMRC: Modified Research Council Dyspnea Scale

significantly improved in female group (vitality p<0.001, physical functioning p<0.001, general health perceptions p=0.036, physical role functioning p=0.001, emotional role functioning p=0.002, social role functioning p=0.006, mental health p=0.01, bodily pain p<0.001). Physical functioning, physical role, mental, pain, vitality was significantly improved after PR in male patients with COPD (p=0.016, p=0.017, p=0.028, p=0.009, p=0.034 respectively). mMRC score significantly improved after PR in both groups (p<0.001 both) (Table 2). HAD anxiety scores significantly improved in both gender after PR (p<0.05 both). While HAD depression scores improved in female patients after PR, no statistically significant improvement was observed in male patients (p=0.002, p=0.9; Table 2).

When we compare the gains after PR between the two groups, the decrease in dyspnea perception and the decrease in depression scores were statistically significantly higher in female patients (Table 3). Also HAD depression score change and SF36 'emotional role' score change (Δ) was significantly higher females compared to males (Table 3).

DISCUSSION

This study showed that PR has had a positive effect on many outcome measures including exercise capacity and dyspnea scores, regardless of gender. After PR, there was a significant betterment in quality of life in women with COPD. Furthermore, the improvement in depression scores for female

participants could not be observed in male participants.

The prevalence and incidence of COPD among women is rapidly increasing (16). Therefore, women with COPD could be a new target for clinicians in pulmonary medicine. Also, there are demographic differences between male and female COPD patients. Firstly, the etiology of COPD may be different in female COPD patients (6). The rate of smoking and the amount of smoking is usually heavier in male patients with COPD. However indoor air pollution may be an etiological factor for women patients with COPD (6). In the present study males were heavy smokers compared to female COPD patients. Although in recent years rate of smoking is increasing in women, indoor air pollution and biomass exposure is still important in many countries (2). Recognizing the growing prevalence of COPD in women is urgently necessary in order to promote worldwide improvements in disease management including pulmonary rehabilitation for half of the population.

When searching the impact of COPD in women, the studies showed that with the same FEV1% values female showed lower disease-related quality of life, higher degrees of dyspnea, worse exercise performance compared to men. They also showed poorer functional and psychological status compared to male patients (17,18). To overcome these biases between genders we matched 1 female to 1 male participant with similar distributions of observed covariates. In our study, female patients with COPD benefit in terms of perception of dyspnea, psychological and general health status and exercise capacity. Therefore, the gains after PR shows that with the same severity of the disease women with COPD tend to gain similar benefits compared to male patients after PR. To adequately evaluate the effects of treatment in real-world settings, significantly more thorough evaluations of these components and precisely conducted prospective trials are required.

Although the gender differences in outcomes of cardiac and stroke rehabilitation have been shown in studies, it is not clear if the outcomes are different in women with COPD after pulmonary rehabilitation (19,20). In a systematic review investigating gender differences in 11 studies after PR showed that half of the studies showed similar gains in men and women for outcomes such as exercise capacity, dyspnea and psychological status (21). In our study, women with COPD benefit in terms of all the above three outcome.

In two study's authors described that woman showed lower anxiety scores than men after PR but similar gains in overall functional status for both sex (22,23). In the study by Ninot et al., both genders tended to benefit similarly from completing a PR program regarding these outcomes (24). In this present study similarly with the mentioned studies, many expects of health status improved after PR in women with COPD, but also depression and anxiety scores significantly improved after PR. We believe that the etiology of depression and anxiety may be different in women with COPD and therefore it may not be improved after PR. However, studies with more women participants are needed in order to find out the reason of this outcome after PR in patients with COPD.

Consisting literature reported that women with COPD reported more severe dyspnea. From a big COPD cohort, DeMeo et al. suggested that among 4,387 patients with COPD, both younger (OR1.94 95% CI 1.60–2.36) and older women (OR 1.38, 95% CI 1.11–1.71) showed more severe dyspnea, compared to men (25). Also, women with COPD reported higher MRC dyspnea scores at baseline in the TORCH study (26). In our study we showed that women with a median mMRC score of 3, had greater benefits in dyspnea perception compared to men after PR. Therefore, we believe that; prescribing PR for women with COPD may be a complementary treatment in dealing with dyspnea.

In many countries including our country the rate of reaching and successfully completing a PR program is low. A study from our country showed that the rate of patients prescribed PR between 2008 and 2016 was between 0.32% and 0.59% among all registered patients with COPD (27). So still only below 1% of all COPD patients had the chance to start a PR program. Also mentioned study reported that number of man (n = 60,852, 62.1%) was higher than that of women with COPD (n = 37,018, 37.8%) (27). So, it can be clearly seen that female patients with COPD have a very low rate of starting a PR program. In this study we showed that female COPD patients have clear and certain gains after PR similar or even better compared to male COPD patients. So, we believe that for clinicians dealing with COPD prescribing PR to women COPD patients should be taken into account.

CONCLUSION

This study showed that PR had a positive effect on many outcome measures, regardless of gender. Female patients benefited more from the program in reducing the perception of dyspnea and improving the depression score. However, guidelines for COPD regarding PR did not mention any gender related difference in recommendations. We believe that studies including more participants, the effect of gender related differences on the outcome of PR program, are needed to be clarified.

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