Gender and COPD in Patients Attending a Pulmonary Clinic*

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**Objectives:** To compare gender differences in the clinical expression of COPD patients attending a pulmonary clinic.

**Materials and methods:** We compared 53 FEV₁-matched men and women with COPD attending a pulmonary clinic. We studied age, smoking pack-years history, \( P_{aO_2} \), \( P_{aCO_2} \), functional residual capacity, body mass index (BMI), dyspnea, 6-min walk distance (6MWD), health-related quality of life, presence of comorbidities, and exacerbations in the previous year.

**Results:** Women were younger (57 years vs 65 years, \( p < 0.05 \)), smoked less (48 pack-years vs 69 pack-years, \( p < 0.05 \)), had better \( P_{aO_2} \) (74 mm Hg vs 67 mm Hg, \( p < 0.05 \)), lower \( P_{aCO_2} \) (40 mm Hg vs 45 mm Hg, \( p < 0.05 \)), lower BMI (25 vs 28, \( p < 0.05 \)), more exacerbations in the last year (1 vs 0, \( p < 0.05 \)), and fewer comorbidities (Charlson score 2 vs score 4, \( p < 0.05 \)) than men. Even though women had the same FEV₁, better oxygenation, better \( P_{aCO_2} \), and fewer comorbidities, they performed poorer in walking distance (6MWD percentage of predicted, 87% vs 105%; \( p = 0.05 \)), had worse quality-of-life scores (Saint George’s Respiratory Questionnaire [SGRQ] symptoms score, 51 vs 41, \( p < 0.05 \); SGRQ activity score, 58 vs 47, \( p < 0.05 \)), and had a higher degree of dyspnea (Modified Medical Research Council scale > 2, 28% vs 6%, \( p = 0.05 \)).

**Conclusions:** In a population of patients with COPD attending a pulmonary clinic, there are gender-related differences in the clinical expression of COPD that need further attention.


**Key words:** clinical presentation; COPD; gender

**Abbreviations:** BMI = body mass index; GOLD = Global Initiative for Chronic Obstructive Lung Disease; 6MWD = 6-min walk distance; MMRC = Modified Medical Research Council

The influence of gender on the expression of COPD has received limited attention. Gender differences in airway behavior and in the clinical manifestations of airway disease occur throughout life and are thought to be related to biological as well as sociocultural factors.1–3 As Becklane and Kauffmann3 point out, “In population-based studies of airway disease, gender is considered a standardizing variable rather than one worthy of investigation in its own right.” The lack of information regarding gender and COPD is surprising because according to COPD disease surveillance in the United States,4 there was a fivefold increase in the mortality rate due to COPD in women between 1971 and 2000. In the latter year and for the first time, the number of women dying from this disease surpassed that of men (59,936 vs 59,118). In the United Kingdom during the period from January 1990 to December 1997, the prevalence of physician-diagnosed COPD in women outpaced that of men.5 The prevalence of cigarette smoking in women is approaching that of men, and women live longer than men.

The limited data available, mostly epidemiologic, suggest that there may be true gender-related differences.1–13 A better characterization of the gender-related expressions of the disease could help identify differences, if they exist, in the natural history, physiologic expression, and clinical behavior of the disease in women. In addition, the information could be used to design therapeutic approaches that are tailored to the gender-specific differences. This study was conducted to describe possible gender differences in the clinical expression of COPD in a cohort of stable patients with the disease.
MATERIALS AND METHODS

This FEV₁-matched case series study recruited COPD patients attending the pulmonary clinic at Hospital Universitario Ntra Sra de Candelaria, a tertiary public university hospital in Spain, from January 2000 to June 2004. We recruited 53 consecutive women attending the clinic and then matched 53 patients with similar degree of airflow obstruction randomly selected from our much larger population of men with COPD. Patients with all degrees of airflow severity were included if they had smoked ≥ 10 pack-years and had a postbronchodilator FEV₁/FVC of < 0.7 after 400 µg of inhaled albuterol. Patients were excluded if they had a history of asthma and/or the FEV₁ increased > 12% or 200 mL after bronchodilator, or had a history of bronchiectasis, tuberculosis, or other confounding diseases. The patients were clinically stable (no exacerbation for at least 2 months) at the time of the evaluation and were part of the population studied for the BODE multicenter study.14 The Ethical Committee of the Hospital approved the study, and all patients signed the informed consent.

We evaluated the study sample using proven prognostic parameters for COPD patients: age, degree of airflow obstruction by FEV₁, dyspnea by the Modified Medical Research Council (MMRC) scale,15 exercise capacity by the 6-min walk distance (6MWD),16 and health-related quality of life by the Saint George’s Respiratory Questionnaire (SGRQ).17 We also evaluated the presence of comorbidities by the Charlson scale, in which the higher the score, the more comorbidities are present,18 and the exacerbations in the previous year of the study date.

Postbronchodilator FEV₁, FVC, and FEV₁/FVC were determined by spirometry using the European Community for Steel and Coal for Spain reference19 (MasterLab 920; Jaeger, Wurzburg, Germany). Body mass index (BMI) was calculated as the weight in kilograms divided by height in meters.5 Arterial blood gases were measured at rest. Exacerbations were defined as episodes of increased dyspnea, production of phlegm, and cough that required medical attention, differentiating those that required medical admission and those that did not for one full year.

The 6MWD was performed following the American Thoracic Society guidelines,16 using as reference values those of Troosters et al.20 Functional dyspnea was measured using the American Thoracic Society-modified MMRC.15 Health status was determined using the language-specific validated SGRQ questionnaire that provides three individual domain scores: symptoms, activity, impact (psychosocial dysfunction). A total score is calculated, with zero indicating no impairment and 100 representing maximum impairment.17

We describe each variable using mean ± SD or median (25 to 75th percentiles), depending on their distribution. We explored for differences between genders in each parameter using Student t test for variables with approximately normal distribution, Mann-Whitney U rank test for variables without normal distribution, and Fisher Exact Test or Pearson χ² test for nominal and categorical variables.

We describe the matching method as follows: we took our matched patients from an initial sample of 87 male and 53 female COPD patients; we were able to match every female patient with a male patient with FEV₁ percentage of predicted ≥ 2%; when more than one male patient matched, we randomly chose the patient to be included in the final sample, being blind to the rest of the evaluated parameters.

RESULTS

Were able to match 53 men and women. The patients were white. When enrolled, 75% of the men and 73% of the women were still smoking. None of the patients had a history of exposure to biomass fuel. Using the Global Initiative for Chronic Obstructive Lung Disease (GOLD) staging system,21 and representing men and women, respectively, they were distributed as follows: stage I, none; stage II, 47% vs 47%; stage III, 45% vs 45%; and stage IV, 8% vs 8%.

Table 1 shows differences between the matched population of men and women for the studied parameters. Women were younger and smoked less than men. There were no differences in current smoking status (75% men and 73% women). Women had a lower BMI, and a higher percentage had a BMI ≤ 21. Women had fewer comorbidities and more exacerbations in the previous year than men. Women had a higher PaO₂ and a lower PaO₂ than men. No differences were found in functional residual capacity. Even though they had the same predicted FEV₁ and better mean PaO₂, women had a lower 6MWD in percentage of predicted values and reported more dyspnea. Women also scored worse in all of the domains of the SGRQ (total, 44 vs 34, p = 0.08; symptoms, 50 vs 45, p = 0.03; activity, 53 vs 48, p = 0.04; impact, 31 vs 23, p = 0.24), as shown in Figure 1.

DISCUSSION

The main finding of the study is that when matched for FEV₁, men and women with COPD

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Men (n = 53)</th>
<th>Women (n = 53)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>65 ± 8</td>
<td>57 ± 11</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Pack-years</td>
<td>69 ± 27</td>
<td>48 ± 28</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>28 ± 4</td>
<td>25 ± 7</td>
<td>0.04</td>
</tr>
<tr>
<td>BMI ≤ 21, %</td>
<td>5</td>
<td>32</td>
<td>0.007</td>
</tr>
<tr>
<td>Charlson scale, points</td>
<td>4 (2–7)</td>
<td>2(1–3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>6MWD % of predicted</td>
<td>105 ± 22</td>
<td>87 ± 18</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>PaO₂, mm Hg</td>
<td>67 ± 9</td>
<td>74 ± 11</td>
<td>0.001</td>
</tr>
<tr>
<td>PaCO₂, mm Hg</td>
<td>45 ± 6</td>
<td>40 ± 5</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Functional residualcapacity, %</td>
<td>140 ± 31</td>
<td>135 ± 32</td>
<td>0.520</td>
</tr>
<tr>
<td>6MWD, m</td>
<td>518 ± 92</td>
<td>444 ± 85</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>MMRC points, %</td>
<td>94</td>
<td>72</td>
<td></td>
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</tbody>
</table>

*Data are presented as mean ± SD or median (25 to 75th percentile) unless otherwise indicated.
attending a pulmonary clinic present with different clinical manifestations of the disease. Several studies\(^1\)–\(^{13}\) have suggested gender differences in the diagnosis and clinical manifestations of COPD. Women are less responsive to long-term exercise therapy,\(^8\) score lower in quality-of-life questionnaires,\(^9\) manifest more reactive airways,\(^10\) and report more dyspnea for the same degree of airflow obstruction\(^11\) than men. Women also appear to have better prognosis when they start oxygen therapy.\(^12\)

To our knowledge, there is only one published study\(^{13}\) specifically designed to compare the clinical differences between men and women with COPD. Gift and Shepard\(^{13}\) compared physiologic (spirometry, arterial blood gases) and clinical characteristics (symptoms) in a population of 48 women and 56 men with very severe COPD. They reported that women were younger and had more COPD-related symptoms such as dyspnea, cough, and wheezing than men.

Our study expanded these observations. We incorporated additional important outcome variables, some known to predict outcome of the disease: BMI, 6MWD, and health status. We also compared exacerbations in the last year and comorbidities, variables affecting the clinical evolution and the socioeconomic consequences of the disease. All these variables were not included in the work reported by Gift and Shepard.\(^{13}\)

The first interesting finding in this study was that women attending our pulmonary clinic were younger than men by approximately 8 years for the same degree of airflow obstruction. This observation, similar to that reported by Gift and Shepard,\(^{13}\) suggests that COPD becomes clinically more evident in women at an earlier age than it does in men. This is interesting because most health practitioners do not consider COPD when evaluating symptomatic younger patients, particularly if they are women.\(^6\)

Our results suggest that COPD in women may run a longer clinical course than that observed in men.

In our study, women smoked significantly less than men (48 pack-years vs 69 pack-years), likely due to the younger age and probably shorter smoking history. The fact that women have same lung function at a younger age with a lower smoking history is not unique to our study. The same observation has been reported by others\(^{1}–{^{3}}\), which lends support to the concept that woman may be more susceptible to the noxious effects of inhaled smoke.

One important finding of our study not previously reported is that for the same GOLD stage, women have fewer comorbidities than men, explained by the fact that men were older than women and have more often hypertension, diabetes, and cardiovascular diseases. We consider this important because women with fewer comorbidities expressed more dyspnea, walked less, and had worse quality of life than men independent of any other concomitant diseases. We attribute the more intense respiratory symptomatology as due to a more intense expression in women of their respiratory disease.

Women had more exacerbations than men. However, there were no differences in the rate of hospitalization. This may imply that even though women have more symptomatic exacerbations of the disease that requires medical attention, these were not severe enough to require hospital admission. This finding confirms the more symptomatic expression of the disease in women with the importance that this has in the socioeconomic consequences of the disease.

In this population, with the same predicted FEV\(_1\), PaO\(_2\) was significantly higher in women than in men. PaO\(_2\) in COPD patients is important because it predicts survival,\(^{22}\) the development of pulmonary hypertension, and determines the need for ambulatory oxygen therapy. Also, levels of PaCO\(_2\) were lower in women, another important prognostic factor in COPD patients.\(^{23}\) Our findings may help explain why women with COPD live longer than men in general and particularly those receiving oxygen therapy.\(^{12}\)

BMI independently predicts mortality in COPD.\(^{24,25}\) In our patients, BMI values in women were lower than that in men with the same FEV\(_1\). Although the median values for both genders were still normal, when compared with published values for the Canary Islands\(^{26}\) the women were statistically thinner in the same age range (normal values for BMI: men, 27; women, 29). Also, mortality has been
shown to sharply increase when the BMI drops below 21,23 a value observed in 32% of our women vs 5% of men (p < 0.05) for the entire population. All these findings suggest that COPD may affect the nutritional status of men and women in a different way, with the women appearing more susceptible to the effect of the disease.

6MWD is also an independent predictor of mortality in COPD.27 It is known that the 6MWD of normal women is some 84 m lower than that of men.20 However, when expressed as a function of their predicted value, the women in our cohort walked 87% compared with men who walked 105% of their predicted value. Interestingly, the values were within the normal predictive range, suggesting that our population does not have impairment in this functional domain, an interesting finding since we do not expect patients with COPD to have a normal value for 6MWD. The finding that patients in Spain have relatively better walking distance than patients from the United States was also reported in another study,14 indicating that patients with COPD from Spain may have less impairment in this domain or that there is a need to develop predictive values for the 6MWD in different areas of the world.

For the same degree of obstruction, more women manifested higher MMRC scores than men, confirming previous findings11 that women express more dyspnea for the same degree of obstruction. This is very interesting considering that dyspnea is an important survival prognostic factor for the disease26 and affects the quality-of-life scores.

Our study also showed that for the same predicted FEV1, women scored worse in all the domains of the SGRQ. Even though only the symptoms and impact domains reached statistical significance, women scored higher than men by > 4 points, the threshold considered to be clinically significant, in all of the different domains. This supports the finding of previous studies9 and raises the question of the its meaning, since it is considered an important prognostic factor for COPD.29

There were some limitations in this study. First, our patients were recruited from those attending a pulmonary clinic and therefore may not represent the COPD population at large. Second, our findings in women may only be applicable to patients with cigarette smoke-related COPD and not to patients with COPD due to biomass fuel.30 However, cigarette smoke-related COPD constitutes the most frequent cause of the disease in the world. Third, knowing that women have more hyperactive airway than men,31 the exclusion of patients with symptoms of asthma or a positive bronchodilator response may have biased our population and results in terms of losing important information about the population of women with a “twitchy airway” that may have been included in studies with less strict exclusion criteria. However, we wanted to establish uniform noncontroversial diagnostic criteria independent of gender. If anything, the differences between men and women may have been even greater had we included more patients with hyperactive airways. As has been reported recently,32 having asthma increases by 12-fold the risk for COPD.

Taken together, our findings indicate the following: in patients attending a pulmonary clinic for COPD, when we compared women and men with the same degree of obstruction (GOLD stages II and III), women had smoked less, were younger, and had lower comorbidity scores than men. For the same lung function and volumes, women had better oxygenation and lower levels of PaCO2. However, women had more exacerbations, expressed more dyspnea, and had worse scores in all the domains of the quality-of-life questionnaires. We believe that as a new multidimensional expression of the disease is already accepted (obstructive, perceptive, and systemic), our findings support the hypothesis that women may be differentially affected in the perceptive and systemic domains. It seems that for the same degree of obstruction, women perceive symptoms in a different way and have different exercise capacity and nutritional status.

In summary, our results indicate that more attention must be devoted to the characterization of the way in which exposure to inhaled particles (from cigarette smoke or from biomass fuels) affects women. Larger cohort or population studies with a significant number of women exclusively designed to evaluate the effect of gender on the clinical manifestations of COPD are needed.

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