Women with chronic obstructive pulmonary disease: an emerging phenotype of the disease

In the western world, the bulk of the overall increase in chronic obstructive pulmonary disease (COPD)-related morbidity and mortality is driven in part by the increasing burden of disease in women. The high prevalence of COPD among women in the developed world is likely related to the historic increase of smoking among women in these areas. In some developing countries, COPD in women results from the exposure to other toxic inhalants such as biomass combustion products (especially those used in cooking and heating). The clinical presentation of the disease appears to be different in women compared with men, with a greater expression of the perceptive and nutritional domains in females. The differences are seen primarily at the earlier stages of the disease and decrease or disappear as the severity of COPD progresses. Although little is known about the associated co-morbidities in women with COPD, the available information suggests a high prevalence of anxiety and depression. The therapies available for the treatment of patients with COPD have been better studied in men than in women. There is a need for larger and better studies specifically designed to explore the relationship between gender and COPD.

KEYWORDS: clinical presentation ■ COPD ■ gender ■ sex ■ women

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The influence of gender on the expression of chronic obstructive pulmonary disease (COPD) has received limited attention [1–3]. The medical community around the world is witnessing a growing epidemic in tobacco-related diseases in women, mainly COPD and lung cancer [4].

Data from the USA indicate that the absolute numbers of COPD cases, hospitalizations and deaths among women exceeds that of men [5]. A better characterization of gender-related expressions of the disease could help identify differences, if they exist, in the natural history, physiological expression and clinical behavior of the disease in women. In addition, the information could be used to design therapeutic approaches tailored to the gender-specific differences.

In this review we will evaluate the available data focused on sex (biological) and gender (socio-cultural) differences in the prevalence, clinical presentation and treatment response of patients with COPD. Table 1 summarizes the existent available data on gender differences in COPD.

Prevalence & risk factors

The prevalence and mortality of COPD in women is rapidly increasing [5]. Some indirect evidence suggests that smoking women may be more likely to develop lung function impairment and have increased mortality compared with men [1,6]. Epidemiological studies have demonstrated that COPD is not diagnosed in almost 80% of the spirometrically detected cases [7,8]. Although the phenomena occur in both genders, the problem is magnified in women by the fact that the medical community has a gender bias towards the diagnosis of the disease [9,10]. Indeed, a meta-analysis from 28 different countries [11], as well as recent well-conducted epidemiological studies in Latin America [8], China [7] and Japan [12], have demonstrated that COPD prevalence is higher in males even after adjusting for confounding factors such as age and tobacco consumption. In a study of 795 high-risk smokers, our group has demonstrated [13] that for the same smoking history there was a lower COPD prevalence in women, suggesting a lower susceptibility for development of airway obstruction in that gender (Figure 1). To solve this conflicting information, follow-up cohort studies are required to determine the rate of change of the prevalence by gender, as the current generation of smoking adolescents reach adulthood, especially if the smoking prevalence of female teenagers remains intact.

Another issue of particular importance in women is the development of COPD in never-smokers. The data here are, once again, conflicting. A recent analysis from the Third National Health and Nutrition Examination Survey (NHANES III) database [14] demonstrated that even in the population of never-smokers, men

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Table 1. Gender differences in chronic obstructive pulmonary disease.

Men	Women
Higher incidence in epidemiological studies [7,8]	Greater susceptibility to the tobacco effects [1]
High level of underdiagnosis [8]	Underdiagnosis even higher than men [7,8]
	Gender bias in the diagnosis from doctors [9,10]
Emphysematous type more common [11]	Commonly presented with chronic bronchitis [11]
Dyspnea appears later in the evolution [14]	More dyspnea for the same degree of AO [20]
	Greater compromise of their quality of life [42–44]
	Less exercise capacity for same level of AO [20]
	Higher prevalence of hyperactive bronchi [66]
	Higher prevalence of malnutrition [27]
	Higher prevalence of anxiety and depression [45]
Easier to quit tobacco [54]	When tobacco abandoned, greater benefits [54]
Better inhalator technique use [55]	Better initial benefits from IC [57]
Better and prolonged response to PR [61]	Greater psychological benefits from PR [60]
	Better overall survival [52]

AO: Airway obstruction; IC: Inhaled corticosteroids; PR: Pulmonary rehabilitation.

had a higher prevalence of airway obstruction than women (odds ratio: 1.68 [1.08–2.63]; p = 0.02). This was explained at least partially by the preferential occupational air pollution exposure of men. On the other hand, according to WHO, indoor air pollution from solid fuel use (coal or wood, dung and crop residues) for domestic energy is responsible for more than 1.6 million annual deaths, and 2.7% of the global burden of disease [15,16], especially in women. The differences in results may indicate differences in risk exposure owing to cultural and environmental factors.

Whether comparable degrees of cigarette smoking induce greater reductions in lung function in females is controversial [1,3]. Cigarette smoke exposure during childhood and adolescence impairs lung growth more severely in girls than in boys [17]. A recent study has postulated that there may be important sex-related differences in the metabolism (largely mediated by cytochrome P450) of some cigarette smoke constituents, leading to increased production of carcinogenic and airway-toxic molecules in females compared with men [18]. Another theory states that since women have smaller airways, the effects of similar amounts of tobacco or biomass smoke is greater in terms of the development of airway obstruction and the manifestation of symptoms [3]. This is a controversial field where no solid conclusion can be extracted from the available data and clearly demonstrates that additional studies are required.

Clinical presentation

Available data suggest that there are gender differences in the clinical presentation of the disease. These differences were reported mainly from a small cohort of COPD patients from a pulmonary clinic [19], and a recently supported larger cohort of women with COPD and severe emphysema from the National Emphysema Treatment Trial (NETT) [20].

Dyspnea

Our group [19] and others [21] have demonstrated that, compared with men, women with COPD report more functional dyspnea for the same degree of airway obstruction (Figure 2). In our initial study, we observed that dyspnea scores were higher at milder stages of the disease in women than in men. In an attempt to find explanations for that observation, we explored the possible association of several of the respiratory factors thought to be responsible for dyspnea in patients with COPD. Central respiratory drive was the single best predictor of the functional dyspnea scores only in women, whereas other respiratory factors explained most of the variations of the dyspnea scores in men. It is possible that factors such as depression or anxiety (not evaluated in that study and highly prevalent in women with COPD) played a role in the reported differences between genders.

Exercise capacity

Exercise capacity is usually impaired in patients with COPD, mostly when their degree of airway obstruction is severe (forced expiratory volume in one second [FEV_1]% is less than 50% of the predicted value) [22]. The standardized 6-min walking distance (6MWD) is an objective, simple and validated measure of functional impairment [23]. It is known that the 6MWD of normal

women is lower than that of men [24], usually explained by the shorter lower-extremities length of women. In our study, we found that in patients with the same FEV_1%, lower number of co-morbidities and better partial pressure of arterial oxygen, women walked 87% and men 105% of their predicted values, supporting a disproportionate decrease in functional capacity in women with COPD [19]. No information is available at the moment about the predictive power and expected decline of 6MWD in women with COPD. Pinto-Plata *et al.* completed symptom-limited cardiopulmonary exercise tests (CPETs) in 400 patients, with almost equal representation of both genders [25]. In contrast to the results reported for the 6MWD [19], when gender was normalized by the degree of airflow limitation, there was no difference in exercise capacity measured by CPET. It is evident that more research is needed to clarify this important issue.

Nutritional status

In patients with COPD, mortality increases when BMI falls below 21 kg/m^2 [26]. Several observational studies have demonstrated that the prevalence of low BMI (<21) and fat-free mass index (FFMI) (<15) is higher in women with COPD [20,28]. More importantly, the prevalence of low FFMI in patients with normal BMI is proportionally higher in women with COPD [27]. The results suggest that the nutritional evaluation using the BMI or the FFMI should be included alone or integrated in a composite index in the regular assessment of patients with COPD.

Emphysema

A recent large, retrospective cohort study of patients with severe COPD demonstrated that women, relative to men, exhibit anatomically smaller airway lumen with disproportionately thicker airway walls, and less extensive emphysema characterized by smaller hole size and less peripheral involvement [20]. Similar findings were found by Dransfield *et al.* in a cohort from a lung cancer screening program [28]. This anatomical difference may have clinical significance, but it has not yet been fully explored.

Lung hyperinflation

Lung hyperinflation has also been shown to be an important independent predictor of survival [29]. Our group demonstrated that an inspiratory capacity:total lung capacity ratio of less than 0.25 is an independent predictor of all-cause and respiratory mortality, mainly in a population of male patients with COPD [30]. Whether the inspiratory capacity:total lung capacity has a similar power to predict mortality in women remains unknown. In a small sample of women with COPD, we found that the association between inspiratory capacity:total lung capacity and functional dyspnea was similar to that observed in men. We also confirmed that during exercise, the degree of air trapped correlated significantly with the degree dyspnea developed, implying that as has been reported in men, lung hyperinflation plays an important limiting factor in the activities of daily living of women with COPD [31].

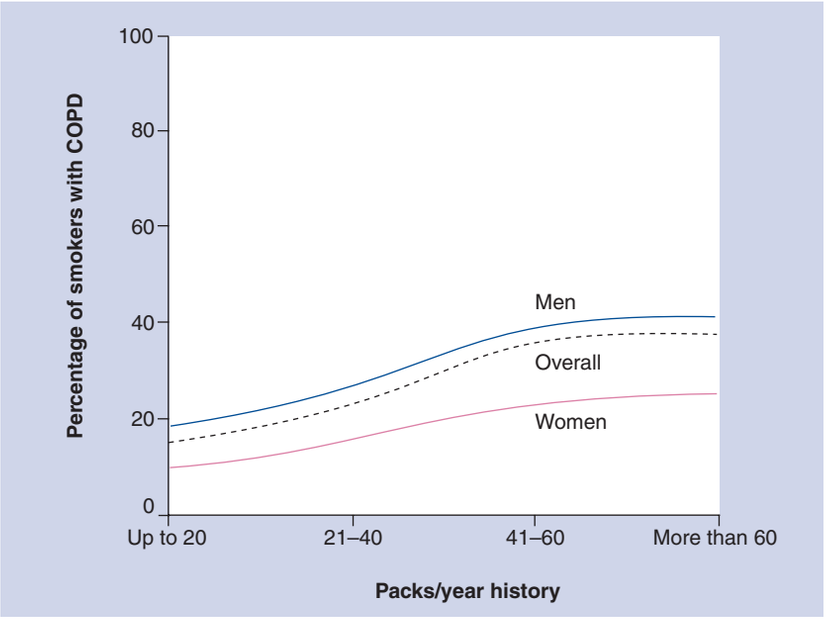

Figure 1. Prevalence of smokers with chronic obstructive pulmonary disease according to the amount of cigarettes smoking history.
Curves show prevalence of men, women and the entire studied population [13].
COPD: Chronic obstructive pulmonary disease.

Exacerbations

It is well known that the majority of patients with moderate-to-severe COPD suffer an average of 1–2 exacerbations a year that cause an important deterioration of their quality of life, lung function and survival [32]. Little is know about exacerbations in women with COPD. Results of a study of men and women with similar FEV_1% demonstrated that women had more episodes of exacerbations than men [19]. However, there was no difference in the rate of hospitalization. Once admitted to a hospital for COPD, women are less likely to die than men [33], but if they require mechanical ventilation the survival rate seems to be lower than that of men [34]. These paradoxical differences require additional studies.

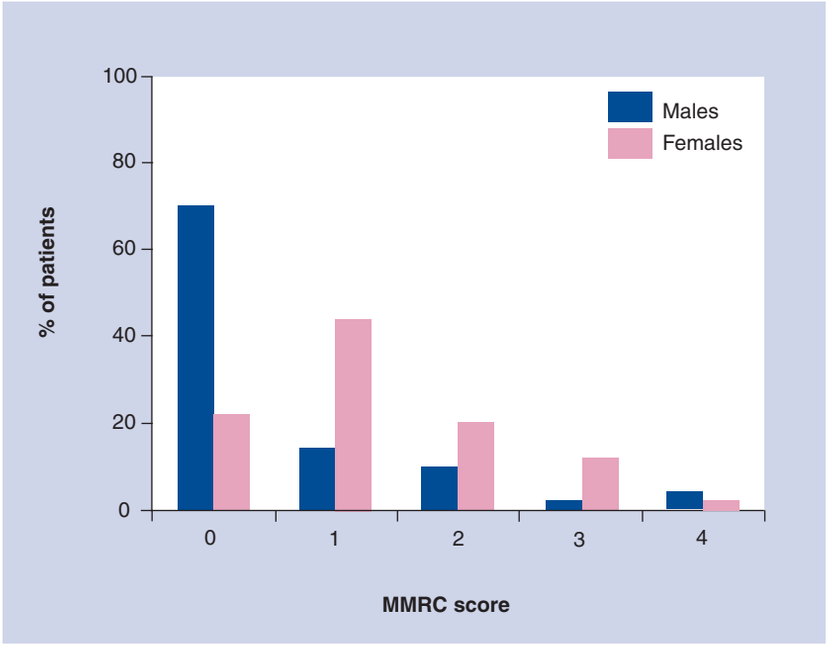

Figure 2. Percentage of patients in each Medical Research Council score category. Women have a greater percentage within the higher categories [31].
MMRC: Modified Medical Research Council.

Quality of life

Quality of life is known to predict mortality [35], hospitalization [36], healthcare resource utilization [35] and response to different treatments [37] in male COPD patients. In the literature there are few reports suggesting a greater impairment in health-related quality of life in female patients with COPD [38–42] (Figure 3). Our group has demonstrated that the relative contribution of the different factors influencing quality of life scores in patients with moderate-to-severe COPD differ by gender [43] (Figure 4). These differences seem to be more pronounced in the milder stages of the disease. Thus, there is consensus that health-related quality of life is more affected in women compared with men. Whether responses to therapies directed at improving health status, such as pulmonary rehabilitation, need to be tailored to programs specifically developed for women has not been explored.

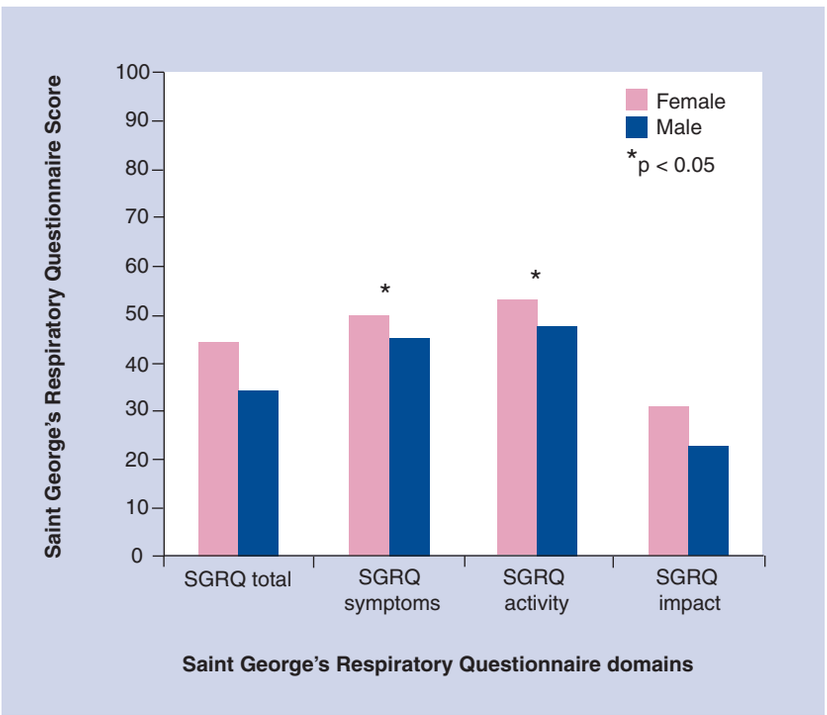

Figure 3. Comparison between mean values of male and female patients, for the different domains of the Saint George´s Respiratory Questionnaire. Statistically significant differences were found in all the domains of the questionnaire [43].
SGRQ: Saint George´s Respiratory Questionnaire.

Anxiety & depression

Psychiatric disorders are nearly two-times more prevalent in women than in men with the disease [44]. Women with COPD have greater psychological distress, worse perceived control of symptoms and greater functional impairment [45]. Co-morbid depressive symptoms in patients with COPD are associated with poorer survival, longer hospitalizations, persistent smoking, increased symptom burden and poorer physical and social functioning [46]. Two small prospective studies in patients with COPD have demonstrated that pulmonary rehabilitation can effectively treat these symptoms and improve patients' quality of life [47,48]. It seems that specific tailored programs, including management of these highly prevalent co-morbidities, should be included in the International Guidelines to properly treat women with COPD.

BODE index

Recently, the multidimensional body mass index, degree of airway obstruction, dyspnea and exercise capacity (BODE) index has been validated in a population of mainly male COPD patients. The BODE index is a better independent predictor of respiratory and overall mortality than FEV_1% [49]. This work was later confirmed by another study [50]. Although the relative contribution that each component of the BODE index has over the total index differs by gender [51] (Figure 5), the score has similar predictive ability in men and women [52]. This property makes BODE a useful index to compare disease severity and results of interventions across genders.

Co-morbidities

Patients with COPD often have other co-morbidities: cardiovascular disease, lung cancer,

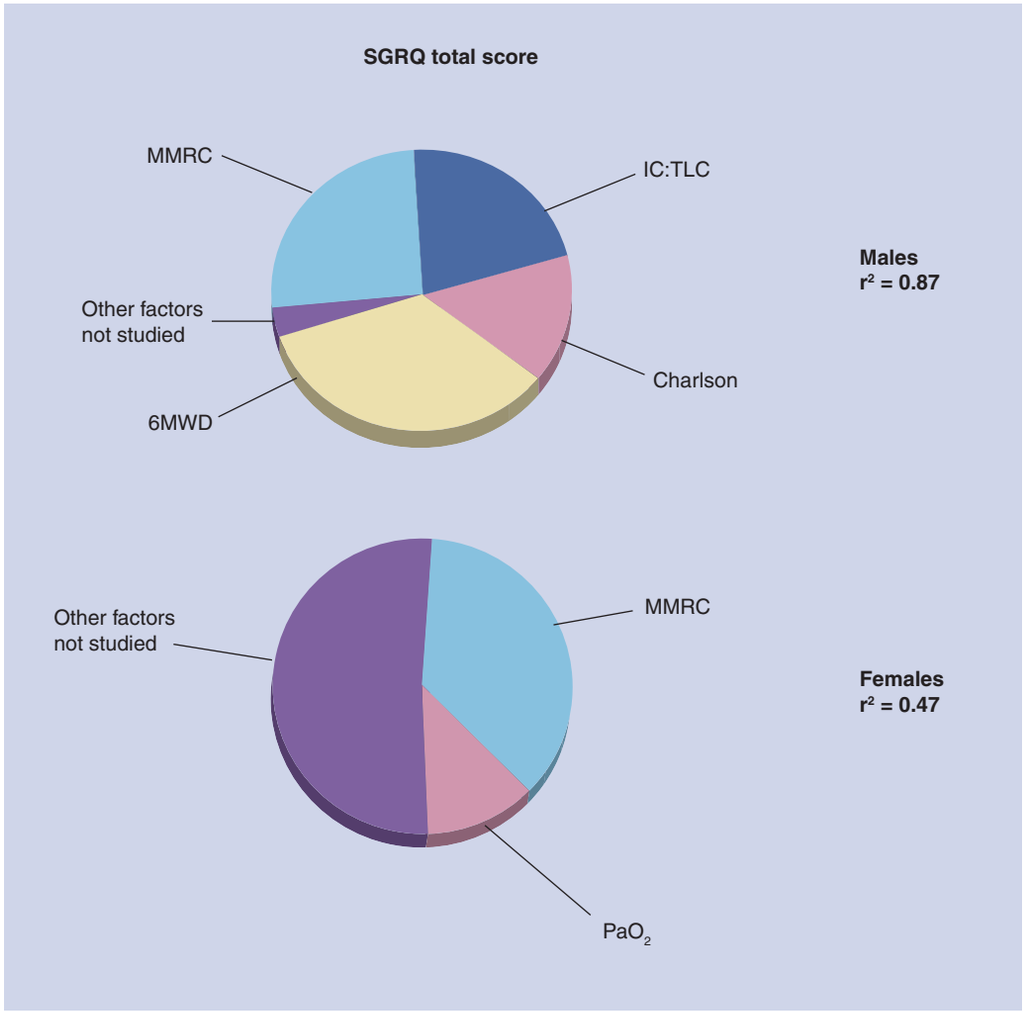

Figure 4. Relative weight of the factors retained in the logistic regression analysis as predictors of the Saint George´s Respiratory Questionnaire total scores for male and female chronic obstructive pulmonary disease patients.
6MWD: 6-min walking distance test; IC:TLC: Inspiratory capacity:total lung capacity ratio; MMRC: Modified Medical Research Council Scale; PaO_2: Arterial oxygen pressure; SGRQ total: Saint George´s Respiratory Questionnaire total score.
Reproduced with permission from [43].

osteoporosis, anemia and the previously mentioned anxiety or depression [53]. Very little is known about the role of gender in the development and prevalence of co-morbidities in patients with COPD. It is logical to think that diseases influenced by the effect of estrogen (like cardiovascular diseases and osteoporosis) are less prevalent during the milder stages of the disease (at younger age), but after the menopause becomes equal to that of men. However, this remains speculative because of the lack of specific information on this topic.

Response to treatment

Tobacco cessation

Connett and colleagues have demonstrated that smoking women have more difficulty quitting their tobacco addiction than men do. Fortunately, if they remain abstinent, women have a greater improvement in the FEV_1 [54]. Tobacco cessation therapies must be individualized and specifically tailored to women, for whom body image and weight are so important. The fact that a high proportion of women with COPD have anxiety, depression or both makes achieving this task even more difficult. Unfortunately, data suggest that tobacco cessation therapy is offered less frequently to women at risk [54]. We should make persistent and intense efforts to decrease tobacco use and improve smoking cessation rates.

Inhalation therapy

Evidence from a small study of patients with COPD suggests that independent of age, women

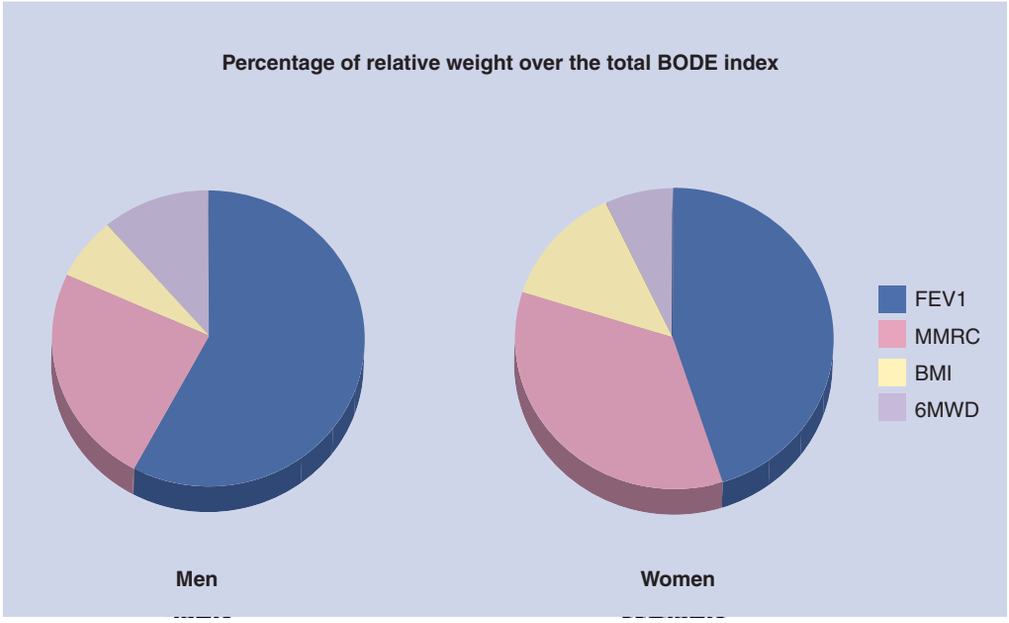

Figure 5. Relative weight that each component of the body mass index, degree of airway obstruction, dyspnea and exercise capacity index have in men and women with the disease.
6MWD: 6-min walking distance test; BMI: Body mass index; BODE: Body mass index, degree of airway obstruction, dyspnea and exercise capacity; FEV1: Forced expiratory volume in one second; MMRC: Modified Medical Research Council Scale.
Adapted with permission from [51].

are much more likely to have an improper multidose inhaler (MDI) technique than men [55]. This is very important at the time of prescribing inhalers to women with COPD, because they may need better education in the use of proper inhalation techniques. Differences in efficacy and safety of respiratory medications by gender are largely unexplored. There are only two studies that specifically address the issue of gender response to inhaled medications [56,57], both of them demonstrating no gender differences. Interestingly, the recently published results of the Towards a Revolution in COPD Health (TORCH) study seem to confirm this finding, as response to therapy was not influenced by gender in over 6000 patients in that study [58].

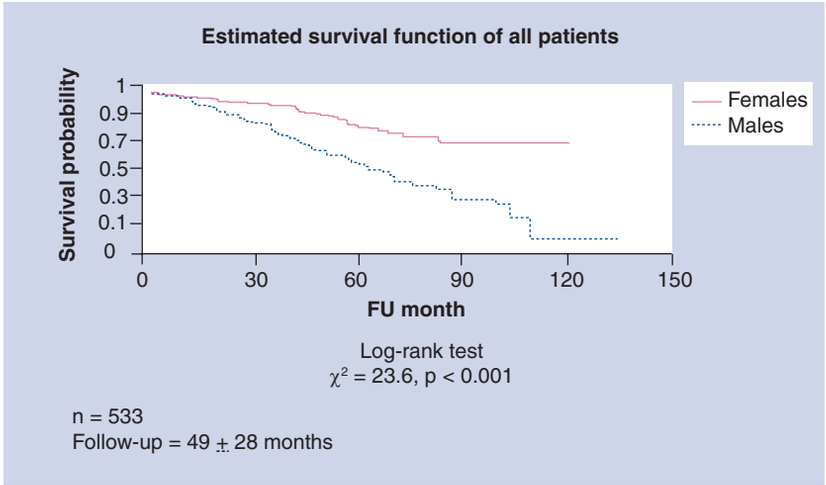

Figure 6. Kaplan–Meier survival curves of the study population by sex.
Log-rank analysis shows that survival is better for the female (83%) than male (76%) population [52].
FU: Follow-up.

Rehabilitation

Pulmonary rehabilitation reduces healthcare resource utilization, improves health status, decreases dyspnea and enhances exercise capacity [59]. Pulmonary rehabilitation is an important component of the comprehensive management of COPD [60], and appears to be equally effective in both genders [61]. Most of the available reports underscore the importance of pulmonary rehabilitation in the treatment of women with COPD, not only for the proven benefits obtained in health status, exercise capacity and dyspnea, but most importantly for the benefit observed in anxiety and depression symptoms [60]. In the trials reported, the benefits were lost over time [61], suggesting that some type of maintenance may be helpful.

Oxygen therapy

Long-term oxygen treatment has been shown to improve survival in hypoxemic patients with

Executive summary

Prevalence & risk factors

- The prevalence and mortality of chronic obstructive pulmonary disease (COPD) in women is rapidly increasing.
- There is a gender bias in the diagnosis of the disease toward the male sex.
- Data suggests that women are more susceptible to the effects of smoke.

Clinical presentation

- Women are more symptomatic for the same degree of airway obstruction.
- Women have a greater compromise of their nutritional status and exercise capacity.
- Women with COPD have a lesser degree of emphysema with central distribution.
- Although they have more exacerbations, they require admission less often, and once admitted they have a better prognosis than men.
- For the same degree of airway obstruction they have a greater impairment of their quality of life.
- The prevalence of depression and anxiety are especially higher in women with the disease, and require further attention.

Response to treatment

- Women have more difficulty quitting their tobacco addiction than men do.
- Women are much more likely to have improper inhaler technique than men.
- Pulmonary rehabilitation programs are indicated in women with COPD, paying especial attention in maintenance therapy.
- No specific information is available in the literature about the possible influence of gender on the available surgical treatments.
- Women had a better survival compared with men with the same degree of severity by body mass index, degree of airway obstruction, dyspnea and exercise capacity (BODE) index and on long-term oxygen treatment.

COPD [62,63]. The differences in response to this therapy between men and women have also been explored [63,64]. Overall survival was better in women on long-term oxygen treatment than in men. However, another recent study reported exactly the opposite – increased mortality in women compared with men [64]. The importance of the topic is such that more studies are required so that resources can be directed to those areas where clear evidence of benefits is demonstrated.

Surgical therapy

No specific information is available in the literature about the possible influence of gender on the available surgical treatments (lung volume reduction surgery and lung transplant) in patients with COPD, and therefore our comments can only be based on opinion. However, the difference in thoracic anatomy, pattern of breathing and gas exchange remain to be explored so that we can best evaluate the response to the different forms of therapy.

Mortality

In population-based studies, women live longer than men [65]. Some studies have suggested that this is also true in patients with COPD [63,64]. Our group recently completed an international multicenter study with more than 500 patients with the disease, and women had a better survival compared with men with the same degree of severity by BODE index and global obstructive lung disease stage [52] (Figure 6). It is important to determine the relationship between gender and COPD outcomes so that we can define gender-specific therapeutic approaches.

Conclusion

Chronic obstructive pulmonary disease is a highly prevalent disease in women around the world. It is mostly a consequence of the exposure to tobacco smoking in the developed countries, and to biomass combustion products in underdeveloped countries. It is an underdiagnosed disease especially in women, and greater efforts have to be made in order to increase COPD awareness. Recent reports have raised the question of the possible higher susceptibility of women to develop the disease and progress more rapidly, but since the information is contradictory and scarce, the medical community has not yet reached a uniform agreement.

The clinical presentation of the disease appears to be different in women compared with men, with a greater expression of the perceptive and nutritional domains in females. It seems that these differences are present mainly at the earlier stages of the disease and tend to decrease or disappear as the severity of COPD progresses. Although there is little information about the associated comorbidities in women with COPD, the available knowledge underscores the presence of anxiety and depression as major problems in women. The therapeutic tools available for the treatment of patients with COPD have been better studied in men than in women. A great effort from researchers, medical personnel and administrators will have to be made to properly address the possible implications of gender differences in the expression of COPD.

Future perspective

There is a growing epidemic of COPD in women that will need increased attention from

the medical community. A great effort from researchers, medical personnel and administrators will be needed to properly address this extra burden on the medical system. There is a lot of work to do in trying to increase the awareness of its diagnosis, clearly define its clinical presentation, adequately tailor the available treatment options and establish public strategies to slow the rapid growth of this deadly disease in women.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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