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REVIEW

Global assessment of the COPD patient: Time to look beyond FEV_1?

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Summary
COPD is a diverse disease entity with multiple dimensions that uniquely define the patient's performance, morbidity and mortality. FEV_1 is both the traditional metric used to define the progression of COPD as well as the strongest spirometric predictor of mortality in COPD patients. However, besides pulmonary functional abnormalities, COPD is also associated with significant systemic effects. Therefore, the global assessment of an affected patient should include different aspects of the consequences of this disorder, beyond the ''gold-standard'' assessment of airflow limitation. Quantification of the patient's dyspnea, body composition as expressed by BMI, simple measures of exercise capacity such as the 6MWD, assessment of comorbidities and identification of characteristics related to different phenotypes are features that may lead to more optimal management of such patients.

Contents

Introduction 651
Simple spirometry 651
Other pulmonary function tests 651
Radiological evaluation 652
Quantification of dyspnea 652
Body composition 652

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Exercise capacity . . . 653
Health-related quality of life (HRQoL) . . . 653
Biomarkers of inflammation . . . 654
Assessment of comorbidities . . . 654
Recognizing different phenotypes . . . 655
Gender differences . . . 655
Smoking habit . . . 655
Exacerbation frequency . . . 656
Emphysema and chronic bronchitis . . . 656
Genomics in COPD . . . 656
Multidimensional grading systems . . . 656
Conclusions . . . 657
Conflict of interest . . . 657
References . . . 657

Introduction

COPD is a major cause of morbidity and disability worldwide and is the fourth leading cause of death in the USA and Europe.[1,2] FEV_1 is both the traditional metric used to define the progression of COPD and the strongest spirometric predictor of mortality in COPD patients.[3] Factors that affect decline in FEV_1 are therefore of prognostic importance in COPD.[4] However, besides pulmonary functional abnormalities, COPD is also associated with significant effects outside the lungs, such as malnutrition, pulmonary hypertension and peripheral muscle weakness, the so-called systemic effects of COPD.[5,6] The negative impact of COPD on patient's quality of life has led to the need of developing alternative tools for the assessment of the COPD patient. It is currently understood that the broad term COPD comprises several clinical phenotypes, including patients with persistent hypoxemia, patients characterized by emphysema and marked hyperinflation, patients with frequent exacerbations, and patients with peripheral muscle dysfunction.[7] The differences between such patients render a more global assessment of COPD imperative. The aim of the present review is to focus on complementary and/or alternative methods of assessment of the individual COPD patients beyond the gold-standard FEV_1, in order to evaluate better the disease severity and predict their prognosis. The parameters that are discussed are the ones that, according to the authors' point of view, are closest to clinical application.

Simple spirometry

Spirometry is the most widely used non-invasive test of pulmonary function and provides an overall assessment of lung function and an objective method for following disease progression or improvement and therapeutic response over time.[8] The post-bronchodilator forced expiratory volume in 1 s (FEV_1) has been used as the gold-standard for the diagnosis and classification of COPD.[2] Furthermore, FEV_1 has been used as a marker for the description of disease severity, and progression.[2,9] FEV_1 is also being used as a marker for evaluating the effect of treatment, although this seems paradoxical since COPD is diagnosed on the basis of a low FEV_1 that is poorly reversible after bronchodilator therapy.[2] The change in FEV_1 following bronchodilator therapy is poorly predictive of improved symptoms and exercise capacity in advanced COPD[10] while several therapeutic agents such as rehabilitation improve symptoms in COPD patients without modifying FEV_1.[11] Post-bronchodilator FEV_1 is more reproducible than pre-bronchodilator values,[12] with an increase of 200 mL plus 12% of the baseline value representing the minimal clinically important difference. Over 50% of COPD patients present significant bronchodilator reversibility, however this response changes with time in a significant proportion of them and does not predict disease progression and response to treatment.[13]

The forced expiratory volume in 6 s (FEV_6) has been proposed as an alternative to forced vital capacity (FVC) that is both reproducible and acceptable for the evaluation of airflow obstruction,[14] and may predict lung function decline in adult smokers.[15] It has been suggested that the FEV_1/FEV_6 ratio may be a more appropriate measure of airflow obstruction than FEV_1/FVC,[16] yet FEV_1/FVC ratio represents a globally accepted measure that has been adopted by current guidelines. Despite the wide criticism over FEV_1/FVC ratio, based on the fact that it may overdiagnose COPD in older populations, data from the Cardiovascular Health Study suggest that a fixed FEV_1/FVC ratio of <0.70 may identify patients who are at greater risk for death and hospitalization from COPD, even among older adults.[17] Based on the above, an FEV_1/FVC ratio <0.70 remains not only the guideline-suggested gold-standard for the diagnosis of COPD, but also a clinically significant measurement.

Other pulmonary function tests

In patients with COPD the loss of lung elastic recoil and development of expiratory flow limitation promote progressive air trapping with an increase in inspiratory capacity (IC). Static lung hyperinflation increases during exercise and has been associated with limitations in the functional capacity of COPD patients.[18] Lung hyperinflation can be evaluated by the inspiratory capacity to total lung

capacity ratio (IC/TLC). It has been shown that the IC/TLC ratio correlates to the patients' dyspnea and exercise tolerance and can be used as a predictor of mortality in COPD.[19] Those findings suggest that the IC/TLC ratio may reflect the overall impact of disease severity and represents a marker that could be useful for the multidimensional evaluation of COPD.[19]

The single-breath diffusing capacity of the lungs for carbon monoxide (DL_{CO}) is frequently used in the differential diagnosis of patients with dyspnea in the clinical setting.[20] The diffusing capacity is a very useful measurement in the assessment of COPD because is the best pulmonary function test which represents the integrity of the pulmonary capillary bed.[21] In the COPD patients, in particular, DL_{CO} correlates with the degree of emphysema on computed tomography of the lung,[22] and may be used as an easily repeatable, non-invasive indicator of the emphysema COPD phenotype. The technique used has been standardized,[23] however a dedicated laboratory with experienced personnel is necessary.[24]

Arterial blood gas analysis is important to determine the presence of hypoxemia and hypercapnia. It is not necessary for all COPD patients, since it is recommended for patients with an $FEV_1 < 50\%$ predicted and symptoms and/or signs indicative of respiratory failure or right heart failure.[2] In that case, it is necessary to determine the patients in need for supplementation of long-term oxygen therapy that will improve their life span.[2] For the rest of the patients, screening with a pulse oximeter is considered as adequate.

Radiological evaluation

Chest X-ray can provide signs that are associated to the presence of COPD,[2] yet in the majority of cases it is not diagnostic for COPD unless obvious bullous disease is present. However, chest X-ray is very important for the exclusion of alternative diagnoses and/or comorbidities, such as heart failure[25] and lung cancer,[26] both being common in smokers, and therefore it may be recommended in the initial evaluation of a COPD patient. In contrast, computed tomography of the chest is not routinely recommended for COPD patients. However, it has been shown that the severity of emphysema varies among patients with the same stage of COPD,[27] and given the fact that high resolution computed tomography (HRCT) scans can detect earlier disease than airflow obstruction or changes in diffusing capacity[28] it may be helpful for the diagnosis of early stages of COPD in patients with preserved lung function.[28] Additionally, chest HRCT is necessary for the diagnosis of upper lobe distribution of emphysema and the referral of patients for lung-volume reduction surgery.[1,2]

Quantification of dyspnea

Dyspnea is a subjective perception of respiratory discomfort and is a result of multifaceted mechanisms, which include abnormalities in the respiratory control system, neurochemical receptors, ventilation, respiratory muscles and gas exchange.[29] Dyspnea is another variable that needs to be determined in primary care, because it is closely related to patients' life and for that reason the evaluation of dyspnea should be included among standard measures of physiologic lung function.[30] Dyspnea can vary among patients with the same degree of airway obstruction as differences in languages, in races, cultures, gender, and in the manner in which concepts or symptoms are held can all influence the idea, quality and intensity of dyspnea.[29] Categorizing patients with COPD on the basis of the level of dyspnea has been shown to be a better predictor of 5-year survival than the classification on the basis of disease severity, as assessed by the percentage of predicted FEV_1.[31] Furthermore, categorization on the basis of the level of dyspnea gives a better estimate of disability and health-related quality of life in COPD patients.[32,33] Finally, it has been shown that the initial degree of dyspnea of a COPD patient is determinative for its improvement in exercise performance and health status after a program of pulmonary rehabilitation.[34] Therefore, the level of dyspnea, in addition to the level of airway obstruction, may provide clinically important information in the management of patients with COPD.[31]

There are several ways to assess dyspnea in clinical practice, while it takes only a few minutes and can be easily evaluated while taking patients' history. The estimation of the level of dyspnea during activities of daily living can be achieved by using several clinical dyspnea ratings. The ones more commonly used in clinical practice is the modified Medical Research Council (MRC) scale for the evaluation of dyspnea in everyday activities (Table 1)[35] and the Borg scale for the quantification of dyspnea on exertion.[36] Finally, the assessment of the influence of dyspnea on health-related quality of life can be evaluated using a disease-specific questionnaire such as the St. George's Respiratory Questionnaire.[37]

Body composition

One of the most common consequences of COPD is the nutritional abnormalities that present as weight loss and skeletal muscle loss and dysfunction.[38] Some of the main potential mechanisms of skeletal muscle mass loss and dysfunction in COPD include physical inactivity due to

Table 1 The modified Medical Research Council dyspnea scale (MMRC).[35]

Grade of dyspnea	Symptoms
Grade 0	Not troubled by breathlessness except on strenuous exercise
Grade 1	Short of breath when hurrying or walking up a slight hill
Grade 2	Walks slower than contemporaries on the level because of breathlessness or has to stop for breath when walking at own pace
Grade 3	Stops for breath after walking 100 m or after a few minutes on the level
Grade 4	Too breathless to leave the house or breathless when dressing or undressing

shortness of breath, tissue hypoxia (which suppresses protein synthesis), systemic inflammation (which increases muscle cell apoptosis) and increased levels of oxidative stress (especially during disease exacerbations) which causes muscle fatigue and facilitates proteolysis.[38]

The body mass index (BMI, which is calculated as weigh/height squared in kg/m^2) is an established independent prognostic factor in COPD, and a lower BMI (i.e. less than 21 kg/m^2) is associated with greater risk of death irrespective of the stage of the disease.[39,40] COPD patients with mild to moderate COPD have better prognosis if they are normal or overweight, whereas in severe COPD being overweight and even obese is associated with a better survival.[39] Changes in BMI also seem to have an impact in survival, as it has been observed that weight loss in COPD is an independent risk factor of all cause mortality, while weight gain seems to have a protective effect in underweight and normal-weight subjects with severe COPD.[41]

The body mass can be divided into two compartments: fat mass and fat free mass (FFM). The first serves as a metabolic inactive energy store, whereas the latter contains the metabolic active organs, among which skeletal muscles are the largest part.[42] Body composition can be determined with several methods such as measurement of bioelectrical impedance (BIA), dual-energy X-ray absorptiometry (DEXA), or underwater weighting. It has been proposed that BIA has a better precision among non-obese patients and DEXA in obese patients.[43] Importantly, alterations in body composition can occur in COPD patients in the absence of clinically significant weight loss, and include loss of fat free mass and bone mineral content.[38] Low FFM (i.e. less than 16 kg/m^2) is common in patients with COPD and is related to greater mortality, even in patients with normal BMI.[42,44] Furthermore, the decline in FFM in COPD patients is associated with worse lung function and frequent exacerbations.[45] The fat free mass index (FFMI, which is calculated as FFM/height squared) reflects better the skeletal muscle mass in patients with COPD and has been recently shown to correlate to dyspnea, airways obstruction and exercise capacity.[46] In support of those observations, another study has shown in a cohort of 162 COPD patients that a simple measurement of quadriceps strength represents a better predictor of mortality compared to age, FEV_1 and BMI.[47] BMI still represents the easiest measurement, yet an evaluation of body composition and/or skeletal muscle strength may provide additional information and identify individuals in need for nutritional support and exercise intervention.[48]

Exercise capacity

Patients with COPD frequently report dyspnea related to everyday tasks and are markedly inactive in daily life.[49] This symptom-induced inactivity is an additional factor that leads to deconditioning and muscle weakness.[50] Several laboratory tests are available for the objective evaluation of functional exercise capacity, such as the cardiopulmonary exercise testing, the Shuttle Walk Test and the 6-minutes walking test. Cardiopulmonary exercise testing is considered the gold-standard in the evaluation of patients with pulmonary diseases as it is monitoring breath by breath several cardiopulmonary variables, including maximal oxygen uptake, pulmonary output of CO_2, minute ventilation, and cardiac frequency.[51] However, cardiopulmonary exercise testing requires dedicated laboratory equipment and expertise, therefore it cannot be suggested for everyday clinical practice.

In the past years, simpler tests of exercise capacity have been implemented in the evaluation of COPD patients. In the Shuttle Walk Test the patient walks around a 10-m circuit at a pace set by an audible signal, that is ramped up each minute. The end-point is the distance that the patient has walked when they can no longer keep pace with the signal.[52] However, the test that has gained importance globally in the assessment of patients with COPD is the 6-minute walk test, which has proven to be reliable, safe and easy to apply.[53] The primary measurement of this test is the total distance that can be walked in 6 min; secondary measures include oxygen saturation which is measured via pulse oximetry, as well as dyspnea and fatigue that are measured using a Borg or a visual analog scale.[54] The 6-minute walking distance (6MWD) has been shown to be an independent predictor of mortality in COPD patients, as shorter walked distance was confirmed to be associated with a higher mortality.[55] A recent report from the same group has shown that the 6MWD declines over time and that this decline is most important in patients with severe airflow limitation (i.e. $FEV_1 < 50\%$ predicted).[56] Interestingly, in patients with severe COPD the decrease in FEV_1 over time has been shown to be relatively small,[56] suggesting that decline in exercise capacity occurs independently from changes in lung function.[55] According to the above, it is clear that 6MWD can help describe clinical changes that are not detectable with the use of pulmonary function tests alone, especially in severe and very severe COPD.

Health-related quality of life (HRQoL)

Health-related quality of life (HRQoL) is a subjective measurement based on an individual perception of alterations in life satisfaction due to problems with health. In patients with advanced lung disease, HRQoL reflects the impact of the disease and its management, in combination with the existing comorbidities, on the ability of a person to perform or enjoy activities of daily living.[57] Over the past years, more and more research has been undertaken in order to quantify the impact of disease on daily life and well-being of COPD patients. The main instruments used to evaluate HRQoL are the Medical Outcomes Study Short Form 36 (SF-36) and St George's Respiratory Questionnaire (SGRQ), a generic and a disease-specific Questionnaire, respectively.[37,58]

HRQoL outcomes are very important in all aspects of COPD because they are felt to represent changes that are clinically most relevant to patients and that may not be measurable by other more conventional parameters.[59] Impaired exercise performance and functional capacity are quite strongly associated with poorer health status.[60] Several factors may have effect in the HRQoL. For example, patients with abnormally low or high body weight, as well as patients with low lean mass, were found to have poorer

HRQoL.[61] Despite the fact that patients with more severe COPD tend to present with worse HRQoL,[62] the correlation between health status, as expressed by the SGRQ, and FEV_1 in COPD patients is weak; however, it has been reported that the total score in SGRQ can be attributed to a combination of cough, wheeze, MRC dyspnea grade, 6MWD, and anxiety score.[60] Moreover, health status measurements are associated to exacerbation frequency, reflecting the impact of exacerbations on COPD patients' everyday life.[63] Finally, health status questionnaires have been used for the assessment of the effect of treatment interventions in prospective clinical trials.[64] The minimal clinically important difference in the SGRQ that is related with a clinically significant reduction in symptoms and the impact of the disease on a patients' daily life is a change of 4 units.[60] According to the above, health status questionnaires can bring together a wide range of effects of COPD into one comprehensive measure. However, they are time-consuming for the busy clinician to perform and they represent currently mainly research tools.

Biomarkers of inflammation

COPD is associated with both airway and systemic inflammation.[4] Airway inflammatory markers are higher in more severe disease and increase during COPD exacerbations.[4] However, despite the widespread use of exhaled biomarkers in patients with asthma and their use in clinical practice,[65,66] no exhaled biomarker has been widely used in clinical trials in COPD. In contrast, there is evidence that shows that systemic inflammation is present in stable COPD and that the intensity of the inflammatory process relates to the severity of the underlying disease.[67] Several inflammatory markers such as C-reactive protein (CRP), fibrinogen and IL-6, are increased in patients with COPD in both stable disease and exacerbations,[4,68,69] with CRP being the most studied biomarker. A study has connected elevated CRP levels with increased resting energy expenditure and reduced exercise capacity,[70] whereas an epidemiologic study from the Copenhagen City Heart Study has shown that CRP is an independent predictor of COPD hospitalizations and death.[68] However, in a recent prospective cohort study of patients with moderate to very severe COPD followed-up for a median of 36 months, CRP was not significantly associated with survival.[71] Despite the fact that COPD is a systemic disease and has recently been suggested to be a part of a chronic systemic inflammatory syndrome,[72] no systemic biomarker can be suggested yet for the routine evaluation of COPD patients, with CRP being the single possible exception for the time being. However, CRP is neither specific nor sensitive for the evaluation of COPD. Future longitudinal studies in well-characterized COPD patients are warranted in order to identify possible biomarkers that will help in the characterization of different phenotypes of the disease and predict disease progression.[73]

Assessment of comorbidities

COPD patients are to great extent elderly, former or current smokers, with increased systemic inflammation,[74] factors that are associated with significant comorbid diseases such as cardiovascular disease, osteoporosis, cancer and depression.[74] Several studies have shown that patients with COPD present more comorbidities than matched controls without COPD[75] and these comorbidities account for a significant part of health-care utilization.[76] We are about to discuss some of the most frequent comorbidities which may influence the outcome of COPD patients.

The association between COPD, systemic inflammation and cardiovascular mortality is very important since more than one half of all patients with COPD die from cardiovascular causes and lung function is a predictor of all cause and cardiac specific mortality.[77] It is known that COPD increases the risk of cardiovascular disease (i.e. atherosclerosis, ischemic heart disease, stroke and sudden cardiac death) by two- to three-fold and it has been suggested that persistent systemic inflammation that occurs in COPD may contribute significantly to the pathogenesis of the cardiovascular abnormalities observed in COPD patients.[25] Interestingly, COPD patients present with increased risk for cardiovascular morbidity and mortality especially at younger age.[78] COPD patients should be evaluated for cardiovascular disease with the use of echocardiogram, while pulmonary artery catheterization may be used in cases where pulmonary hypertension is suspected. Transthoracic echocardiography may be problematic in COPD patients because hyperinflation limits its diagnostic accuracy.[79] Furthermore, non-invasive assessment of coronary artery disease in COPD by stress testing is difficult to evaluate since such patients are limited by dyspnea on exertion. Pharmacologic testing (including adenosine and dipyridamole) may be associated with bronchoconstriction and may also be avoided.[79] When coronary disease is suspected in COPD patients the diagnosis must be confirmed with the use of invasive methods.

Osteoporosis is increased in patients with COPD, and has multiple possible causes, including malnutrition, sedentarism, smoking, steroid treatment and systemic inflammation. Incidence of osteopenia and osteoporosis are both increased in more severe disease, and they are invariably present in patients with low BMI and FFMI.[80] Recently, COPD has been recognized as an independent risk factor for the identification of osteoporosis in men.[81] Additional risk factors include increased age and lower body weight and a predictive model including the above three variables has been proposed.[81] Male COPD patients who are over 55 years of age and/or weight less that 70 kg (154 lb) should undergo a dual-energy X-ray absorptiometry testing and receive therapy according to its result.[81] The effects of the presence of osteoporosis in COPD patients are not only the predisposition to painful vertebral fractures and the disability costs, but also the impact in lung function by altering the configuration of the chest wall. It has been estimated that each thoracic vertebral fracture results in a 10% decrease in vital capacity.[52] Therefore, in cases in which osteoporosis is likely to occur it is crucial to evaluate and treat it properly.[52]

It has been shown that COPD is an independent risk factor for lung cancer and that smokers who develop COPD are in greater risk for lung cancer compared to smokers without COPD.[26] Chronic inflammation may play a role in the pathogenesis of lung cancer as a tumor promoter by up-regulating pro-oncogenes, and down regulate suppressor

oncogenes there by inhibiting apoptosis and inducing cell transformation.[82] The risk for development of lung cancer in COPD patients remains elevated for years after smoking cessation.[82] According to these observations COPD patients are a possible target group that should be screened for the early detection of lung cancer.[26]

Another frequent comorbidity in COPD patients is the development of depression. It is a fact that COPD patients often face major physical impairment and embarrassing symptoms, including chronic dyspnea.[83] Patients with severe COPD are in even greater risk of developing depression.[83] The diagnosis and treatment of depression in COPD patients are important, as depression by itself is aggravated by worsening dyspnea and fatigue, diminishes functional performance and exercise capacity and is associated with impaired quality of life.[84] A recent study has shown that frequent exacerbators present higher depression scores compared to infrequent exacerbators.[85] Recognizing and treating depression, besides improving quality of life, may also indirectly decrease the risk of exacerbations, since depressed patients have more difficulty to learn and comply with treatment plans.[86] Furthermore, treating depression may also improve the outcome of acute exacerbations, as it has been shown that depressed patients do not seek medical help early, which leads to increased risk for poorer outcomes.[86] Several tools have been used to assess depression in patients with chronic diseases, including the Hospital Anxiety and Depression Scale and the Depression anxiety stress scale which have been validated in COPD patients.[87,88] COPD patients with physical disability, severe dyspnea, and poor quality of life, as well as those receiving long-term oxygen therapy and those of low socioeconomic status, are more susceptible to develop depression.[88]

Gastroesophageal reflux disease is common in patients with severe COPD and a significant proportion of those patients did not present symptoms or receive appropriate treatment.[89] Higher BMI was the only predictor of the presence of Gastroesophageal reflux disease in those patients.[89] Furthermore, in a recent study, gastroesophageal reflux symptoms were associated to the occurrence of COPD exacerbations.[90]

Anemia represents another significant comorbidity in severe COPD patients, and it is surprisingly even more prevalent than polycythemia.[91] Anemia is related to the level of dyspnea and reduced exercise capacity in COPD patients, whereas it is a predictor of survival in cohort studies of severe COPD patients.[91,92] The mechanism of anemia development in COPD might be similar to that in other chronic diseases, possibly related to erythropoietin resistance.[92]

Comorbidities, especially cardiovascular, osteoporosis, and depression, represent significant aspects of the global management of the COPD patient in primary care. Those complex comorbidities are also more likely to present in COPD patients who are admitted to hospital compared to patients without COPD.[93] It is not clear whether comorbid conditions make COPD patients more susceptible to the consequences of COPD, or whether COPD increases the patient's susceptibility to those specific comorbidities.[82] However, it is important to treat them aggressively in patients with COPD, having in mind that most clinical practice guidelines do not modify or discuss the applicability of their recommendations for older patients with multiple comorbidities.[94]

Recognizing different phenotypes

COPD is a complex disease, including different types of patients under the broad definition of chronic airflow limitation that is not fully reversible and is produced by an inflammatory response of the lungs to inhaled noxious particles or gases.[2] However, in clinical practice the disease does not present as a single entity and the identification of different phenotypes may be important for clinical decisions.

Gender differences

Among the latest years, the prevalence and mortality of COPD in female smokers seem to increase.[95] Recent studies have shown that disease manifestations differ between men and women.[96,97] Women with severe emphysema tend to develop COPD at a younger age and usually have shorter smoking history compared to men with disease of the same stage.[97] In a study of 53 male and 53 female COPD patients matched for FEV_1, despite the fact that they had less comorbidities and better arterial blood gases (i.e. higher PaO_2 and lower PCO_2), female patients presented with lower BMI, worse exercise capacity, more impaired health-related quality of life and a higher degree of dyspnea compared to male patients.[96] Furthermore, the risk of death seems to be higher in women with severe COPD using long-term oxygen therapy (LTOT) compared to men.[98]

The gender differences among COPD patients do not concern only the symptoms of the disease but also the different effects of several therapeutic interventions. For example, a meta-analysis has shown that inhaled corticosteroids have more beneficial effects in women,[99] whereas a randomized clinical trial revealed that women present little added benefit to long-term over short-term exercise therapy compared to men.[100] The above findings suggest that gender should be taken into account in the everyday assessment of COPD patients; further studies are needed in order to identify interventions that may improve gender-related outcomes.

Smoking habit

Tobacco smoke represents the most important risk factor for the development of COPD.[2] COPD patients who continue to smoke have a more rapid decline in FEV_1,[101] and are in greater risk of developing lung cancer compared to COPD patients who quit smoking.[102] Current smokers present also had higher levels of systemic inflammation (as expressed by serum CRP levels) compared to ex-smokers,[103] and have a greater risk for hospital admission.[104] Furthermore, former smokers with COPD benefit more from the use of inhaled corticosteroids, presenting lower all-cause mortality.[99] Importantly, a combination of a long-acting β_2-agonist and an inhaled corticosteroid exhibited more prominent anti-inflammatory effects in ex-smokers compared to current smokers.[105] According to the above,

the assessment of the smoking status of COPD patients is necessary and smoking cessation interventions should be promptly discussed with the primary care physician.

Exacerbation frequency

Exacerbations of COPD (ECOPD) are an important feature in the natural history of COPD and it is important for the attending physician to identify the frequency of these events and to recognize the factors that may be associated with them.[106] It is well known that several risk factors are associated with AECOPD, the most important being a history of hospital admission for ECOPD, comorbidities, HRQoL,[107] more severe disease[108] and lower airway bacterial colonization.[109] ECOPD have a deleterious impact on COPD patients, that is reflected on dramatic impairments of HRQoL.[110]

According to the number of ECOPD per year, COPD patients can be considered as frequent exacerbators, with different studies using different cut-off points of exacerbations per year.[111,112] It has been shown that frequent exacerbators have a significantly greater decline in FEV_1,[111] and they present higher mortality risk, especially those requiring hospital admission.[112] Despite the fact that the majority of the evidence-based therapeutic interventions proposed by the current guidelines are effective in the reduction of ECOPD,[1,2] the identification of COPD patients who present frequent exacerbations is important, since those patients are at greater need for more aggressive treatment.

Emphysema and chronic bronchitis

The most commonly discussed phenotypes of COPD are the well-known images of the patients characterized predominantly by emphysema (the ''pink puffers'') and the patients characterized mainly by the presence of chronic bronchitis (''blue bloaters''). The ''blue bloaters'' are usually characterized by hypoxemia and hypercapnia, which are complicated by pulmonary hypertension and right heart failure; the ''pink puffers'' are characterized by cachexia, quite normal blood gases and greater dyspnea. Despite the fact that emphysema can occur in both phenotypes, it is more frequently observed in the ''pink puffer''.[113] The introduction of high resolution computed tomography (HRCT) has brought a new dimension to the study of COPD, as it offers the opportunity to study the pathologic processes involved in structural changes within the lung and to investigate the severity, extension and distribution of the lung destruction.[7,114] Besides the well-studied aforementioned features of the two phenotypes, recent studies have studied the differences between patients with and without emphysema on HRCT; COPD patients with HRCT-confirmed emphysema are characterized by more severe lung function impairment, more intense airway inflammation and possibly more serious systemic dysfunction.[115] Further longitudinal studies are needed in order to assess the impact of the two phenotypes on the outcome of COPD patients.

Genomics in COPD

It is generally accepted that cigarette smoke is the major cause of COPD.[2] However, the fact that only 20% of smokers will develop COPD shows that the disease develops from a gene-environment interaction.[2] Furthermore, population studies have shown a familial aggregation of lung function and COPD clustering within families.[116] Plenty of research has been devoted to the identification of genes that are implicated in COPD development. To date α_1-antitrypsin deficiency is the only documented genetic risk factor and is related to early COPD onset.[117] Serum α_1-antitrypsin levels should be evaluated in patients with minor smoking history and/or early disease onset (i.e. $<$45 years) as well as in those who have a family history of the disease.[2] A number of other genes have been proposed to be implicated to COPD development, such as matrix metalloproteinase (MMP)-9, MMP-2, tumor necrosis factor-α, transforming growth factor-β and superoxide dismutase.[117] However, since the results of genetic association studies are largely inconsistent, and the role of those genetic variants in COPD development has not been definitively identified, the detection of alterations in such genes cannot be suggested for application in clinical practice yet.

Multidimensional grading systems

A multidimensional disease, such as COPD, needs multidimensional grading systems in order to describe better the health status of the individual patients and define better their prognosis.[40,113] A staging system which was recently reported is the BODE index, a composite measure that incorporates body composition (Body mass index), airflow limitation (Obstruction, expressed by the FEV_1% predicted), Dyspnea (expressed with the modified MRC scale), and Exercise capacity (as expressed with the 6-minute walking distance).[40] The method for performing the scoring of the BODE index is easy and does not require special equipment (Table 2). The score ranges from 0 to 10, increasing with disease severity, and has been shown to be a good predictor of hospitalization as well as of all cause and respiratory mortality in COPD patiens.[40,118] Exacerbations have significant Impact on the BODE index[119] and increases in the BODE index are associated with mortality in severe COPD.[120] The latest findings support that the BODE index can be a practical instrument for outcomes assessment of COPD that may be easily implemented in clinical practice.

Table 2 Variables and point values used for the computation of the multidimensional BODE Index.[40]

Variable	Points on BODE index			
	0	1	2	3
FEV_1 (% of predicted)	$\geq$65	50–64	36–49	$<$35
Distance walked in 6 min (m)	$\geq$350	250–349	150–249	$<$149
MMRC dyspnea scale	0–1	2	3	4
Body mass index (kg/m^2)	$>$21	$\leq$21		

FEV_1: Forced expiratory volume in 1 s; MMRC: modified Medical Research Council.

Table 3 Variables that may be useful for the global assessment of the COPD patient, both in the clinical and in the investigational level.

Type of assessment	Clinical	Investigational
Pulmonary function tests	Post-bronchodilator FEV_1, FEV_1/FVC ratio	DLCO, IC/TLC
Dyspnea	MMRC scale	Borg scale
Body composition	BMI	FFM, FFMI
Exercise capacity	6-Minute Walk Test, Shuttle Walk Test[a]	Cardiopulmonary exercise testing
Radiological evaluation	Chest X-ray	HRCT (necessary for referral for LVRS)
Quality of Life	SGRQ	SF-36
Comorbidities		
	Cardiovascular disease	Anemia
	Osteoporosis	Gastroesophageal reflux disease
	Depression	
	Lung cancer	
Phenotypes		
	Smoking habit	Gender
	Exacerbation frequency	Presence of emphysema

FEV_1: Forced expiratory volume in 1 s; FVC: Forced expired vital capacity; DLCO: Diffusing lung capacity for carbon monoxide; IC: Inspiratory capacity; TLC: Total lung capacity; MMRC: Modified Medical Research Council; BMI: Body mass index; FFM: Fat free mass; FFMI: Fat free mass index; 6MWD: 6-Minutes walking distance; LVRS: Lung-volume reduction surgery; SGRQ: Saint George respiratory Questionnaire; SF-36: Study short form 36.

[a] Depends on availability.

Conclusions

COPD is a diverse disease entity with multiple dimensions that uniquely define the patient's performance, morbidity and mortality. Therefore, the global assessment of an affected patient should include different aspects of the consequences of this disorder, beyond the ''gold-standard'' assessment of airflow limitation (Table 3). Quantification of the patient's dyspnea, body composition as expressed by BMI, simple measures of exercise capacity such as the 6MWD, assessment of comorbidities and identification of characteristics related to different phenotypes are features that may lead to more optimal management of such patients. Biomarkers represent attractive options but are far from implementation in COPD. Longitudinal studies including properly characterized patients are needed in order to identify which of the aforementioned features are more important for the outcome of COPD patients.

Conflict of interest

None of the authors have a conflict of interest to declare in relation to this work.

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