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REVIEW / DERLEME

Updates in Chronic Obstructive Pulmonary Disease for the Year 2014

Kronik Obstrüktif Akciğer Hastalığı 2014 Güncellemeleri

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Abstract

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality in the world. Research conducted over the past decade has contributed much to our current knowledge of the pathogenesis and treatment of COPD. Additionally, an evolving literature has recently accumulated information about the management of COPD and also about exacerbations. This article reviews a concise summary on the updates in COPD including 1) new pathogenic mechanisms and therapeutic targets, 2) management of patients in Group B, C and D according to GOLD 2014 report; 3) prevention and management of exacerbation; 4) monitoring of natural history; and 5) essential but usually forgotten parts of the management.

KEY WORDS: COPD, disease management, exacerbation, natural history

Özet

Kronik obstrüktif akciğer hastalığı (KOAH) tüm dünyada en önemli morbidite ve mortalite nedenlerinden biridir. Son dekatta yapılan araştırmalar KOAH patogenezi ve tedavisi hakkındaki mevcut bilgilerimize çok katkıda bulunmuştur. Ayrıca son zamanlarda KOAH'ın yönetimi ve alevlenmelerle ilgili giderek artan bir literatür birikimi oluşmuştur. Bu özet derlemede KOAH patogenezinde altta yatan inflamatuar havayolu obstrüksiyonunu daha iyi anlamamıza katkıda bulunacak yeni mekanizmalar ve yeni tedavi hedefleri; çok bileşenli hasta sınıflandırma sistemi ile KOAH yönetiminde yeni bir yaklaşım getiren 2011-2014 güncellenmiş GOLD raporuna göre KOAH'da doğru tedaviyi seçme; alevlenmelerin tanım, önlenmesi ve tedavisi ile ilgili tartışmalı konular; KOAH doğal seyrinin değerlendirilmesi, fenotipler ve biyobelirteçlerin bu değerlendirmedeki rolleri ve KOAH'da çoğunlukla ihmal ettiğimiz sigara bırakma ve fizik aktivite gibi temel tedaviler alt başlıkları gözden geçirilmiştir.

ANAHTAR SÖZCÜKLER: KOAH, patogenez, alevlenme, doğal seyir

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NEW MECHANISMS AND THERAPEUTIC TARGETS IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Chronic Obstructive Pulmonary Disease as an Inflammatory Disease

Chronic obstructive pulmonary disease (COPD) is associated with chronic inflammation of the airways and lung parenchyma that is characterized by increased numbers of neutrophils, activated macrophages, and activated T-lymphocytes (Tc1 and Th1 cells) [1]. The inflammation is amplified in COPD compared with smokers without COPD, and the molecular basis for this amplification is now better understood, providing novel targets for future therapies. Macrophages are markedly increased in COPD, and these cells play a key role in recruiting other inflammatory cells and in releasing mediators and proteases. Macrophages in the lungs are recruited from circulating monocytes by chemotactic factors such as CXCLI (GRO-α) and CCL2 (MCP1). The inflammatory changes in COPD are due to the release of multiple inflammatory mediators, including lipid mediators, cytokines, and chemokines [2]. Many of these mediators are regulated by the proinflammatory transcription factor nuclear factor- κB (NF-κB), which is activated in epithelial cells and macrophages of COPD patients [2]. Activated macrophages and neutrophils release elastolytic enzymes, particularly matrix metalloproteinase (MMP)-9, that contribute to the development of emphysema. In addition, cytotoxic Tc1 cells may induce the destruction of alveolar cells. Small airway narrowing and fibrosis appear to be the major mechanisms contributing to airflow limitation and air trapping, but the mechanisms of fibrosis are poorly understood. Th17 cells may play a role in orchestrating neutrophilic inflammation in COPD [3].

Corticosteroid Resistance

In sharp contrast to asthma, the inflammation in COPD shows little response to corticosteroids. This steroid resistance may be explained by the reduced activity of a key nuclear enzyme, histone deacetylase 2 (HDAC2), which also accounts for the

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amplified inflammation in COPD [4]. The reduction in HDAC2 is driven by increased oxidative stress through the activation of the enzyme phosphoinositide-3-kinase-δ (PI3Kδ), which is inhibited by low concentrations of theophylline [5]. Clinical trials with low dose theophylline as a means of reversing corticosteroid-resistance in COPD are currently underway.

Reduced Bacterial Phagocytosis

Alveolar macrophages normally phagocytose inhaled microorganisms and keep the respiratory tract sterile, but in COPD, there is a defect in bacterial phagocytosis by macrophages that may result in chronic bacterial colonization [6]. There is a similar defect in the uptake of cellular debris and apoptotic cells, such as neutrophils (efferocytosis), resulting in impaired resolution of inflammation [6]. We are now able to reverse this defect with novel drugs as the signaling pathways have been defined.

Accelerated Lung Aging

COPD represents accelerated aging of the lungs, and this may be due to a defect in anti-aging molecules, such as sirtuin 1 (SIRT1), which is markedly reduced in COPD lungs [7]. Oxidative stress reduces SIRT1 expression, and this results in the increased expression of MMP9 through the acetylation of NF-κB and increased cellular senescence through decreased forkhead transcription factor (FOXO) proteins. This may lead to the development of drugs that block these pathways or sirtuin activators.

COPD Comorbidities

COPD is associated with many comorbidities, including cardiovascular, metabolic, and bone diseases, which may be due to the effects of systemic inflammation as a result of overspill from an inflamed peripheral lung [8]. Many comorbidities are due to accelerated aging, and there is evidence that endothelial precursor cells show increased cellular senescence in COPD as a result of reduced SIRT1 levels [9].

Therapeutic Implications

Identifying the novel molecular mechanisms in COPD has revealed new molecular targets that may lead to more effective therapies in the future. Although there have been great improvements in the development of long-acting bronchodilators, this does not address the problem of chronic inflammation, and there is a pressing need for new and safe anti-inflammatory treatments [10]. Many potential anti-inflammatory treatments for COPD have proved to be disappointing and often dose-limited because of side effects. Another strategy is to reverse corticosteroid resistance in COPD with existing therapies, such as theophylline, or novel treatments, such as inhaled PI3Kδ inhibitors.

CHOOSING THE RIGHT THERAPY IN COPD

Management of Low Risk, Highly Symptomatic Patients

According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2014 guidelines, Group B COPD patients are those with less risk factors for exacerbations but with more symptoms [11]. All guidelines suggest that long-acting bronchodilator therapy should always be considered when COPD patients are symptomatic. There is no evidence to recommend one class of long-acting bronchodilators over another for initial treatment [11]. The choice should depend on the individual patient's perception of symptom relief. According to the GOLD guidelines, the first choice in the pharmacological treatment of group B patients is long-acting betamimetics (LABA) or long-acting anticholinergics (LAMA) [11]. The second option for these patients is a combination of LABA and LAMA. Short-acting betamimetics and/or short-acting anticholinergics are the third option for group B patients. Theophylline may be advised for patients not taking inhaled bronchodilators [11].

The detailed clinical properties of these new GOLD groups are not fully known. One of the most important studies on new GOLD groups is the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study [12]. In this study, group B patients showed the highest prevalence of comorbidities and persistent systemic inflammation [12]. Comorbidities are known to have a direct and significant impact on survival in COPD, and persistent systemic inflammation has recently been shown to increase mortality six-fold, irrespective of the severity of the pulmonary abnormalities present [12]. These observations may have clinical implications for the physicians who follow the COPD patients. They should actively look for comorbidities and systemic inflammation in group B patients [12]. Further research is required to comment more on this subject.

Treatment of Stable COPD Patients in High-risk Groups C and D

According to the GOLD 2014 strategy report, COPD cases with few (group C) and many (group D) symptoms comprise high-risk cases with forced expiratory volume in one second (FEV_1) <50% (C1 for few symptoms, D1 for many symptoms), FEV_1<50% and ≥2 attacks in the previous year or ≥1 exacerbations requiring hospitalization in the previous year (C3 for few symptoms, D3 for many symptoms), and FEV_1>50% but ≥2 exacerbations in the previous year or ≥1 exacerbations requiring hospitalization in the previous year (C2 for few symptoms, D2 for many symptoms) [11]. According to the long-term monitoring of C1 and C2 cases, the number of exacerbations per annum stood at 0.58 and 0.52, respectively, versus 0.89, 1.34, 1.39, and 1.86 in D1, D2, C3, and D3 cases [13]. In the three-year follow-up, there were no deaths among C2 cases, whereas D2 cases showed a high rate of mortality [12]. Particularly in Group D cases, deaths related to cardiac, respiratory, and cancer problems were higher than those in Group C [13].

The GOLD 2014 strategy report recommends either only LAMA or a fixed combination of inhaled corticosteroids (ICS) and LABA (ICS/LABA) as the first choice treatment for Group C patients and an ICS/LABA+LAMA treatment for Group D patients [11]. For alternative choice treatments, LABA+LAMA are recommended for Groups C and D patients; LABA or LAMA combination with phosphodiesterase (PDE) 4 inhibitors for Group C patients with chronic bronchitis, and finally, ICS/LABA or LAMA combination with PDE4 inhibitors for Group D patients with chronic bronchitis [11].

Today's COPD diagnosis and treatment guidelines aim to reduce the symptoms and prevent future risks (frequency of

exacerbations per year, annual decline in FEV_1, and mortality) in high-risk patients in Groups C and D [11]. In studies where the ICS/LABA fixed combination was used as the first choice, there was a clinically and statistically significant reduction in the number of exacerbations [14], a slowdown in annual FEV_1 decline [14,15], a clinically significant 17.5-18.5% reduction in mortality in line with the National Institute for Health and Clinical Excellence (NICE) 2010 guideline (15%) [16], and a reduction in ischemic cardiovascular adverse events [15]. In The Investigating New Standards for Prophylaxis In Reduction of Exacerbations (INSPIRE) clinical trial, which compared the use of only LAMA versus the fixed combination of ICS/LABA in high-risk COPD cases, there was a similar reduction in the number of exacerbations in both groups of medication; however, cardiovascular deaths and all-cause deaths displayed a statistically and clinically significant reduction in the ICS/LABA group [17].

The GOLD 2014 strategy report recommends the LABA+LAMA treatment as the alternative choice treatment in high-risk COPD cases [11]. For this group, there is no study comparing the LABA+LAMA treatment with the ICS/LABA treatment. In this group, the ICS/LABA+LAMA treatment is superior to the LABA+LAMA treatment in reducing serious exacerbations that require hospitalization [18]. In case the first choice treatments fail to reduce attacks in COPD cases with chronic bronchitis and frequent exacerbations (≥2 exacerbations/year), PDE4 inhibitors could be added to the treatment [19,20].

COPD EXACERBATIONS: CONTROVERSIES

Defining COPD Exacerbations

Exacerbations are important events during the course of COPD and have a negative effect on patients in terms of mortality, health related quality of life, and decline in lung function including socioeconomic costs on healthcare resources [21]. According to the report of the first European COPD Audit, there was a high mortality rate in COPD exacerbations; approximately 5% of patients died in a hospital and a further 6% died in the 90 days post admission. Hence, it is of utmost importance to appropriately treat these episodes [22].

An exacerbation of COPD is a clinical event that 1) has no standard, consensus definition; 2) unreported events are common; 3) often occurs suddenly with little or no warning; and 4) is subject to diagnostic uncertainty and is easily confused with pulmonary embolism, congestive heart failure, or pneumonia [23].

Similar to COPD, exacerbations are also heterogeneous, resulting from a susceptible patient experiencing a sufficient trigger. The trigger may be bacterial, viral, both, or neither. Being better able to phenotype exacerbations will make possible better intending provided care to improve exacerbations. We need to know which phenotyping strategy is the best at leading specific management and predicting exacerbation outcomes [21,24].

Initially, COPD exacerbation definitions were developed for studies of antibiotic effects on bacterial exacerbations. The Anthonisen definition is based on the presence of one or more of three cardinal symptoms, including an increase or new onset of dyspnea, sputum production, and sputum purulence [25]. In a broad sense, two different approaches have been proposed about how COPD exacerbations should be defined. One of them based on symptoms alone (symptom-based) and the other is based on symptoms plus an event such as the prescription of medication by healthcare providers or hospital admission for an acute exacerbation (event-based) [26]. An expert panel definition is "a sustained worsening of the patient's condition from the stable state and beyond normal day-to-day variations that is acute in onset and may warrant additional treatment in a patient with underlying COPD" [26]. Several COPD studies have used the definition "a worsening of respiratory symptoms, which required treatment with oral corticosteroids and/or antibiotics" [24]. According to the GOLD strategy report, an exacerbation of COPD (AECOPD) is defined as an acute event characterized by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication [11].

There is considerable evidence that approximately half of all COPD exacerbations identified by symptom worsening are not reported to healthcare professionals for treatment [24]. For this reason, some instruments such as the Exacerbations of Chronic Pulmonary Disease Tool or COPD Assessment Test (CAT) may be useful in reporting and assessing the severity of exacerbations [27,28]. To date, no sputum or plasma biomarker with good sensitivity and specificity has been found that can identify either the presence or severity of an exacerbation. Plasma CRP concentration, in the presence of a major exacerbation symptom, is useful and the most effective among the 36 biomarkers studied in the confirmation of COPD exacerbation [29].

Management of COPD Exacerbation

The principles of COPD exacerbation therapy have not changed for years. Many international COPD guidelines recommend that exacerbation therapy be administered stepwise according to the clinical severity of presentation [11,16]. The three classes of medications most commonly used for COPD exacerbations are bronchodilators, corticosteroids, and antibiotics.

The mainstay of therapy at exacerbation remains an increase in the dose and frequency of short-acting inhaled β2 agonists [11,16,24]. The addition of anticholinergics has the potential for increased therapeutic benefit; however, empirical evidence to support this combination is lacking [30]. Nebulizers and hand-held inhalers can be used to administer inhaled bronchodilators. The choice of delivery method should consider the ability of the patient to use the device and the dose of drug required [11].

Systemic steroids have long been a standard for the treatment of COPD exacerbations; however, the optimal strategy for the dose and administration of these medications continues to be debated. In comparison to placebo, systemic corticosteroids improve airflow, decrease the rate of treatment failure and risk of relapse, and may improve symptoms and decrease the length of hospital stay [31]. Therefore, cortico-

steroids are recommended by all major guidelines in the treatment of COPD exacerbations [11,16]. Recent data suggest that shorter durations (5 days) of corticosteroid therapy are as efficacious as the traditional treatment durations (10–14 days) currently recommended by the guidelines [32].

After the earlier studies of Anthonisen et al. [25], the standard management of an exacerbation consists of oral antibiotics if there is evidence of increased sputum purulence or increased sputum volume. Type 1 exacerbations (those associated with increased sputum volume, sputum purulence, and dyspnea) benefited the most with resolution of symptoms in 63% of the antibiotic-treated exacerbations and 43% of the placebo group. However, patients with type 3 exacerbations (who met just one of the three cardinal symptoms) did not show a significant benefit. In addition to exacerbations associated with increased sputum purulence, antibiotics are recommended in severe exacerbations requiring mechanical ventilation [11]. The choice of antibiotics remains uncertain. At present, most guidelines suggest that initial empirical treatment should be in the form of an aminopenicillin, macrolide, or tetracycline, taking into account guidance from local microbiologists and local resistance patterns [11].

Oxygen with or without ventilatory support is necessary in the presence of respiratory failure. Theophyllines are sometimes added for patients responding poorly to other therapies. Exacerbation management should also include the assessment and management of comorbidities, and an opportunity should be taken to optimize long-term therapies to reduce the risk of future exacerbations [11].

COPD exacerbations may show early recurrence, especially in patients who are frequent exacerbators. There is evidence that exacerbation therapy may prolong the time to subsequent events. Thus, prompt and appropriate management of an exacerbation event will not only have an effect on optimizing recovery but also delay the time to the next event [24]. However, there are less data on the appropriate management of COPD exacerbations according to the best practice guidelines, and these data showed that the adherence to guideline recommendations for COPD patients with an exacerbation is generally lacking. The European COPD Audit (including 16,018 patients from 384 hospitals in 13 countries) showed that there is a wide variation in the management of COPD exacerbation between hospitals and between countries and that only 15.3% of patients fulfilled all recommendations of the GOLD guidelines [33].

Prevention of COPD Exacerbation

We have a wide range of pharmacological (vaccination, long-acting bronchodilators, inhaled corticosteroids, PDE4 inhibitors, mucolytics, bacterial extracts, and long-term antibiotics) and non-pharmacological (smoking cessation, pollution control, pulmonary rehabilitation, long-term oxygen therapy, ventilatory support, and lung volume reduction surgery) interventions available to reduce exacerbation frequency or hospitalization in COPD. Perhaps, the greatest remaining challenge is to establish which patient will benefit from which approach [24].

Pharmacological Interventions

Vaccination: There are no studies that have specifically addressed the efficacy of vaccination on the prevention of COPD exacerbations. Cochrane analysis from the limited number of studies performed showed that inactivated influenza vaccine reduces exacerbations in COPD patients. The size of effect was similar to that seen in large observational studies [34]. There is less evidence for the role of pneumococcal polysaccharide vaccine in preventing exacerbations and hospital admissions in COPD. Subanalyses of the data in a randomized controlled study in COPD patients demonstrated a reduction in the incidence of community-acquired pneumonia in those patients younger than 65 years and with severe airflow obstruction, although no mortality benefit was demonstrated [35].

Long-acting bronchodilators and inhaled corticosteroids: Long-acting bronchodilators (LABA and also LAMA) reduce the frequency of COPD exacerbations. Salmeterol, formoterol, and indacaterol significantly reduced COPD exacerbations compared with placebo in a meta-analysis (17 randomized controlled study, 11871 subjects) [36]. In the Understanding Potential Long-term Impacts on Function with Tiotropium (UPLIFT) trial, 5993 patients were randomized to tiotropium or placebo for 4 years. Although reduction in the rate of decline in FEV_1 was negative, tiotropium is associated with a reduction in exacerbation risk, related hospitalizations, and respiratory failure [37]. The Prevention of Exacerbations with Tiotropium trial in COPD showed that tiotropium is more effective than salmeterol in preventing exacerbations in patients with moderate to very severe COPD [38]. Cochrane analysis (including seven clinical studies, 12223 participants) showed that tiotropium was more effective than LABA as a group in preventing COPD exacerbations and disease-related hospitalizations [39]. Reduction in exacerbation frequency has been found for LABA and ICS, both singly and in combination. In the Towards a Revolution in COPD Health (TORCH) study where patients were followed over 3 years, inhaled fluticasone and salmeterol both reduce exacerbation frequency when administered separately in comparison with placebo. The combination of fluticasone and salmeterol resulted in reduced exacerbation frequency further and also fewer hospital admissions over the study period [40]. Reduction in exacerbation frequency has been also found with other LABA/ICS combinations, such as formoterol and budesonide [11]. The New GOLD strategy document indicates a LABA/ICS combination for patients with FEV_1 below 50% predicted and/or where there is a history of frequent exacerbations. The only head-to-head comparison of tiotropium versus salmeterol/fluticasone has been the INSPIRE study [17]. This study randomized 1,323 patients to salmeterol-fluticasone or tiotropium over 2 years. Exacerbation rates are similar with salmeterol/fluticasone combination and tiotropium. In both the NICE guidelines and GOLD strategy document, LAMA can be used as an alternative to LABA/ICS to reduce exacerbations or in addition to the LABA/ICS combination as a triple therapy. Triple combination therapy (LABA/LAMA/ICS) was examined in the study [18]. This study showed that combining tiotropium with salmeterol/fluticasone improves

lung function, quality of life, and hospitalization rates compared with tiotropium alone in moderate to severe COPD patients; however, it does not statistically influence rates of COPD exacerbation.

Phosphodiesterase inhibitors: A pooled analysis of two large placebo-controlled, double-blind multicenter trials revealed a significant reduction of 17% in the frequency of moderate (glucocorticoid-treated) or severe (hospitalization/death) exacerbations with roflumilast in patients with FEV_1 less than 50%, the presence of bronchitis symptoms, and a history of exacerbations [19].

Long-term antibiotics: There is insufficient evidence to recommend prophylactic antibiotic therapy in the management of stable COPD; however, some recent studies, especially with macrolides, have shown promise. Macrolide antibiotics have an additional anti-inflammatory effect. Azithromycin (once daily for 1 year) when added to the usual therapy has been shown to decrease exacerbation frequency in a study of more than 1500 COPD patients, but significant rates of hearing decrement, antibiotic resistance, and increase in cardiovascular events were reported in patients receiving azithromycin [41].

Mucolytics: The routine use of these agents is not currently recommended. A randomized controlled study had a promising result showing that carbocysteine may reduce exacerbation frequency in selected patients with viscous sputum [42].

Non-Pharmacological Interventions

Smoking cessation: In a large prospective population study in Denmark, previous smokers had a lower risk of hospitalization for COPD compared with current smokers [43]. Denmark study, reported a reduced risk of COPD exacerbations in ex-smokers compared with current smokers when adjusted for comorbidity, COPD severity, and socioeconomic status [44].

Pulmonary rehabilitation, long-term oxygen therapy, and ventilatory support: There are relatively less data showing the effect of non-pharmacological strategies to prevent COPD exacerbations. However, there is some evidence from epidemiological and clinical studies in COPD patients that pulmonary rehabilitation programs, long-term oxygen therapy, and non-invasive ventilatory support [11,24] may reduce hospital admissions and prevent exacerbations, but controlled trials have not yet addressed these issues.

AN OUTLOOK ON THE NATURAL HISTORY OF COPD

How to Assess the Natural History of COPD

COPD has a variable natural history, and all individuals do not follow the same course [45]. The progressive nature of COPD is fundamental and brings the necessity for "assessing the natural history of COPD" to successful management of COPD. The natural history represents how a given disease progresses and develops and includes its prognosis. In this concept, the first and most important study was the classic study by Fletcher et al. [46], which remains an indispensable reference for the natural history of COPD. They performed an eight-year prospective study of working men in London and developed a diagram, frequently termed the "Fletcher-Peto curve" (Figure 1). The Fletcher-Peto model is based on FEV_1 and illustrates the relationship between long-term cigarette smoking, decline in lung function (FEV_1), and life expectancy. The curve showed slower decline in lung function during the earlier stages of the disease [46]. On the other hand, it is known that COPD patients are heterogeneous and that all patients will not follow the same clinical course outlined in the Fletcher–Peto curve. The clinical factors other than airflow limitation, including respiratory symptoms, exacerbations, comorbidities, exercise capacity, and quality of life, are as important as decline in FEV_1 for assessing the natural history of COPD, and they all remain undefined within the curve. Our knowledge about the natural history of COPD has increased drastically in recent years, and we know that the natural history of COPD can be altered in some patients through the use of interventions such as treatment for tobacco dependence, control of exacerbations, treatment of comorbidities, increasing exercise capacity by pulmonary rehabilitation, and appropriate medication for COPD.

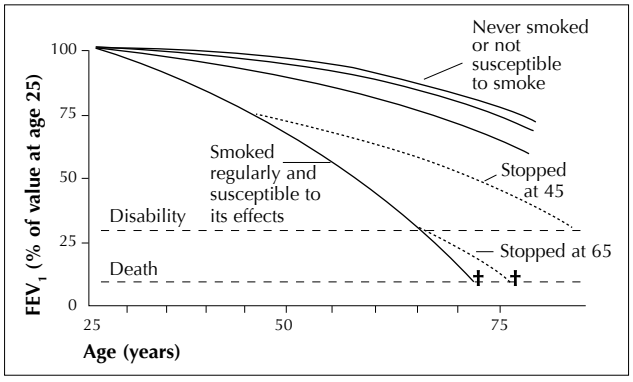

Figure 1. Fletcher-Peto curve [46]

The ways to assess or monitor the natural history of COPD are as follows:

1) Lung Function,
2) Imaging,
3) Respiratory symptoms and quality of life,
4) Comorbidities,
5) Phenotypes and biomarkers.

1) Lung function: Generally, both COPD diagnosis and severity evaluation are based on spirometry, and change in FEV_1 over time is still the most widely accepted measure of disease progression [11]. In the past, more studies were based on only FEV_1, but today it is known that FEV_1 has limitations as it measures only one aspect of the disease and is not predictive of disease progression, especially in early disease; in addition, patients with similar FEV_1 may show very different underlying pathologies and may also be of different functional statuses [45]. Casonova et al. [45] reported that the BODE (body mass index, airflow obstruction, dyspnea, exercise capacity) index is a new and better parameter to predict all-cause mortality compared with changes in FEV_1. These results supported the fact that spirometric assessment alone is insufficient for the characterization of COPD and that more parameters are needed.

2) Imaging: Because spirometry is not sufficient to explain whole nature of COPD, more studies are performed to find new parameters. Computerized tomography (CT) is one of them. The most important parameter to evaluate in CT is emphysema. Recently, it was reported that the level of emphysema predicts all-cause mortality as well as respiratory and cardiovascular mortality in a population-based sample of subjects with and without COPD. Airway wall thickness is associated with respiratory mortality in those with severe emphysema [47]. This is a new point to measure the mortality risk and is substantially important for COPD assessment. There are pros and cons for imaging with CT. More studies are needed to clarify this.

3) Respiratory symptoms and quality of life: Monitoring of symptoms is recommended by most guidelines. The measure of symptoms is subjective because it depends on the patients' perception of disease manifestation. Therefore, assessment of pulmonary symptoms is important to manage COPD. Some indices are recommended to evaluate the symptoms: CAT, Modified Medical Research Council Breathlessness scale, COPD Control Questionnaire (CCQ), and Saint George's Respiratory Questionnaire (SGRQ) [11].

Six-minute walk distance (6MWD) is a test to evaluate the exercise capacity. The ECLIPSE study showed that 334 m in 6MWD is a threshold value to predict mortality and 357 m to predict hospitalization due to exacerbation in COPD patients [48].

Health-related quality of life is another important parameter to manage and understand the natural history of COPD. Because COPD is a systemic, chronic, and progressive disease, it affects the health-related quality of life. These effects are shown in a number of studies using different scales, including SGRQ, Short Form-36, and CCQ [11].

4) Comorbidities: Studies have shown that COPD often coexists with other diseases/comorbidities and that there is a relation between them. The more common comorbidities are cardiovascular diseases, osteoporosis, respiratory infections, anxiety, depression, lung cancer, metabolic syndrome, and diabetes [11]. The comorbidities affect the natural history of COPD. Also, more comorbidities to COPD patients mean an increase of hospitalization risk and mortality [11,49]. Recently Divo M. reported that "Comorbidities are frequent in COPD and 12 of them [oncologic, pulmonary, cardiac, gastrointestinal, endocrine, psychiatric] negatively influence survival. A simple disease-specific comorbidities index (COTE) helps assess mortality risk in COPD patients [50]. Despite studies showing that comorbidities are important in COPD management, they are not included as a measuring parameter in the current COPD guidelines.

In conclusion COPD is a complex disease, and no single measurement can assess the natural history of COPD alone. The combined use of different parameters is better to predict mortality and morbidity.

5) Phenotypes and biomarkers

Is There a Difference in the Natural Course in Different Phenotypes?

COPD is a heterogeneous disease with pulmonary and extrapulmonary manifestations, and patients may have different clinical and radiological features even if they have similar pulmonary function abnormalities [49,51].

COPD phenotypes should be described in order to classify patients sharing similar clinical, radiological, and physiological features with a prognostic value that allows determining the best therapy [51]. We have clinical, radiological, and physiological phenotypes that have been described until now, including chronic bronchitis, asthma–COPD overlap, frequent exacerbators, rapid declines in FEV_1, emphysematous, and systemic phenotypes. However, different methodologies have been used to describe phenotypes such as symptoms, spirometry, nutritional status, quality of life, exercise capacity, biomarkers, induced sputum, CT, employing different statistical analytical methods, and different phenotypes are largely based on cluster analysis [51].

The ECLIPSE study is a very recent example, and it added useful information on our understanding of COPD. This study assessed the validity of specific outcome measures as a descriptor of potential phenotypes [52].

Three different phenotypes with clinical, prognostic, and therapeutic importance have recently been considered by Spanish investigators who guided the Spanish National Guideline of COPD Management as follows: (1) "asthma–COPD overlap," (2) "frequent exacerbator," and (3) "emphysema-hyperinflation phenotype" [51].

The "asthma-COPD overlap phenotype" in COPD is defined as an airflow obstruction that is not completely reversible and that is accompanied by symptoms or signs of increased obstruction reversibility [53]. A history of asthma and/or atopy, reversibility in the bronchodilator test, eosinophilia in sputum, high IgE, positive prick test, and high concentrations of exhaled NO are diagnostic features of the overlap syndrome [51]. The "frequent exacerbator phenotype" is defined as those COPD patients who present with 2 or more exacerbations per year [52]. The ECLIPSE study documented that the strongest predictor of having exacerbations is the previous exacerbation history [52,54]. The hospitalization rate was 7% in GOLD stage II, and it increased to 33% in GOLD stage IV patients of the ECLIPSE cohort [54]. The "emphysema-hyperinflation phenotype" is characterized by the presence of dyspnea and exercise intolerance as the predominating symptoms, which are frequently accompanied by signs of hyperinflation. This phenotype usually has a lower BMI. The degree of dyspnea, intolerance to exercise, and hyperinflation are predictors of mortality [47].

Another possible phenotype is "chronic bronchitis." This phenotype is defined as cough and expectoration for at least 3 months of the year for 2 consecutive years. The prevalence of chronic bronchitis in COPD varies between 14% and 74%. The latest data from the ECLIPSE study has reported a prevalence of 34.6%. The presence of chronic bronchitis is associated with worsened airflow obstruction, progressive lung function decline, and higher exacerbation frequency [55]. Chronic bronchitis is a risk factor for an increased risk of death and hospitalization.

The "persistent systemic inflammation," a novel phenotype, is defined in patients who present with obesity, cardiovascu-

lar disease, diabetes, or systemic inflammation [56]. This subgroup had significantly increased all-cause-mortality and exacerbation frequency.

In conclusion, COPD is a heterogeneous disease, and phenotypes have prognostic and therapeutic significance. This phenotyping approach for COPD could lead to treatments specifically targeted for defined phenotypic groups in the future.

Prognostic Significance of Biomarkers

A biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention. According to the American Thoracic Society (ATS)/European Respiratory Society (ERS) task force, a biomarker refers to the measurement of any molecule or material (e.g., cells, tissues) that reflects the disease process. A biomarker for COPD should have three important properties: 1) repeatability, 2) validity, and 3) should be studied in three groups: COPD, healthy smokers, and healthy nonsmokers [57]. Many clinical parameters tend to be surrogated by biomarkers. These include natural course of the disease, functional status, severity, activity, exacerbation, progression, and mortality. As biomarkers, several sources have been tested so far. Among them, lung biopsies are the most invasive. Induced sputum, exhaled breath condensate, and samples of urine and blood are the other biomaterials.

Biomarkers are also important to monitor treatment effects. "The COPD Biomarkers Qualification Consortium" found that SGRQ-C, 6MWT, and plasma fibrinogen are the most promising markers for different outcomes [58]. Recently, the ECLIPSE study analyzed the repeatability of biomarkers. Fifteen selected biomarkers were studied in three groups comparatively (COPD vs. healthy smokers and healthy nonsmokers). Fibrinogen and CC16 were found to be the most repetitive biomarkers, and CRP was the most variable one. On the other hand, the ECLIPSE study showed that not every COPD patient demonstrated systemic inflammation. They studied the 6 most studied biomarkers [white blood cells, high-sensitivity (hs) CRP, IL-6, IL-8, fibrinogen, and TNF-alpha] in COPD patients comparatively and showed that only 16% of the patients had persistently elevated level of biomarkers. Those patients had the worst outcome, higher exacerbation rate, and higher mortality [56]. In a recent study, Sin et al. evaluated PARC (pulmonary and activation-regulated chemokine)/CCL-18 (CC-chemokine ligand-18) activity in subjects from the Lung Health Study (LHS) and ECLIPSE study in combination with mortality. In LHS subjects, PARC/CCL-18 was related to cardiovascular disease hospitalization or mortality [59]. In another ECLIPSE study, the mortality rate was evaluated in combination with inflammatory biomarkers and clinical indices. Among inflammatory markers, IL-6, neutrophils, fibrinogen, hs-CRP, CCL-18/PARC, and SP-D had an independent significant relation with mortality [60].

In conclusion, studies about biomarkers and mortality have provided conflicting results. In most previous studies, repeatability was not studied thoroughly, and the comparative arms were sometimes missing. The most studied biomarkers were fibrinogen and CRP. Although recent data confirmed that fibrinogen was a good candidate, CRP did not prove to be of much value. IL-6 had the most predictive added power to known clinical indices such as BODE. Some other molecules were arising more specifically from lung inflammation. PARC/CCL-18 and SP-D were the most promising among them. Some other molecules reflecting systemic inflammation and severity were also studied and were found to be related with mortality in an exacerbation setting.

ESSENTIAL PART OF THE MANAGEMENT: THE FORGOTTENS

Smoking Cessation: Is it Necessary in COPD?

Smoking is by far the strongest risk factor of COPD and is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles, tobacco smoke, and other gases [11]. Smoking cessation has been shown to decelerate the progression of the disease and reduce mortality [44,61]. However, most COPD patients may continue to smoke even though they were continuously warned by their physicians. According to several studies conducted in Turkey, smoking prevalence among COPD patients between 16% and 66.9% [62,63].

COPD prevalence is increasing in women at a faster rate than men? However, COPD mortalities are still higher in men than women. Although women take up smoking later than men and smoke fewer cigarettes than men, they can become a COPD patient at a younger age than men [64]. The most well-known Fletcher et al. [46] study demonstrates the association between lung function decline and smoking. Several studies concluded with the same results. However, smoking cessation is the most effective method that slows down the lung function decline in COPD patients [65]. LHS followed smokers with mild obstruction who were randomized to intensive smoking cessation with or without an inhaled bronchodilator compared with smokers in whom no intervention was used. At the end of study, patients who ceased smoking had a markedly reduced decline in FEV_1 over a 5-year period compared with those who did not. In contrast, treatment with a bronchodilator did not significantly affect the decline in lung function over time [66]. Besides reduction in FEV_1 decline, persistent systemic inflammation also tends to decline in ex-smokers [56]. Continuing smoking is also one of the reasons of COPD exacerbations, and smoking cessation in COPD patients reduces hospitalizations and mortality [44,66] and improve symptoms and quality of life. Smoking cessation substantially changes the clinical course of COPD by reducing the rate of decline of pulmonary function and all-cause mortality.

Smoking causes excess mortality, and quitting is effective in all ages and for everybody. Smokers lose at least one decade of life expectancy compared with those who have never smoked, and cessation before the age of 40 years reduces the risk of death associated with continued smoking by approximately 90%. The rate of death from any cause among current smokers was approximately three times that among those

who had never smoked [67]. Some COPD patients quit smoking; however, a large proportion did not quit smoking [68]. COPD patients who continue smoking have special characteristics that hinder their quitting attempts. They smoke more cigarettes daily than smokers without COPD. They inhale the cigarette smoke deeply and retain it for longer in their lungs. The expired air carbon monoxide (CO) levels of smoker COPD patients are higher than those in smokers without COPD. They have a higher degree of physical dependence on nicotine, and they have a lower degree of motivation to quit smoking, low self-efficacy, and low self-esteem levels.

Pharmacological treatments for smoking cessation increase the possibility to quit smoking. Nicotine replacement therapies that include bupropion and varenicline as the first line drugs are used in smoking cessation treatments. These treatments can be used according patient's clinical features and needs. Some smokers with COPD do not want to make a serious attempt to quit. However, clinicians should provide these patients with an adequate treatment. With a good clinical approach, possibilities of success in the quitting attempt of COPD patients can increase. The main success factors for patients with chronic diseases are adherence to treatment and long-term maintenance of the recommended behavior changes. Using a combination of behavioral support and medical therapies may increase the chances of COPD patients giving up smoking successfully [11,69].

Recommendation about Physical Activity in COPD

COPD is a disabling airway disease with variable extrapulmonary effects that may contribute to disease severity in individual patients. Physical inactivity in daily life is a prominent feature in COPD patients [11]. Lower levels of physical activity in daily life are related to a higher risk of hospital readmission and shorter survival in COPD [70,71]. Inactivity contributes to a further worsening of the physical condition of the subject and to even more dyspnea. Although hyperinflation is a compensatory mechanism that increases expiratory flow, it has several disadvantages such as loading the inspiratory muscles and increasing the work of breathing. This contributes to a downward spiral of inactivity, deconditioning, and dyspnea [11,72]. Reduced physical fitness may lead to a shift in patients' lifestyle with low daily physical activity levels inducing a vicious circle of decreased exercise tolerance, which in turn further reduces activity levels and increases social isolation and depression. COPD patients at all stages of the disease seem to benefit from exercise training programs, showing improvement with respect to both exercise tolerance and symptoms of dyspnea and fatigue [11]. Assessment of the amount and intensity of physical activity in daily life is considered very important because of the close relationship between activity levels and health. Physical activity in daily life can be considered "the totality of voluntary movement produced by skeletal muscles during every day functioning" [71]. Physical activity in daily life can be quantified by direct observation, assessment of energy expenditure, and use of physical activity questionnaires and motion sensors [71]. Motion sensors are instruments used to detect body movement, which can be used to objectively quantify physical activity. These devices basically include pedometers (measurement of steps) and accelerometers (detection of body acceleration). The use of pedometers has been promoted to stimulate and monitor walking in the general population because it is suggested that 10000 steps per day are effective for prevention of disease and promotion of a healthier lifestyle [71]. The majority of moderate–very severe COPD patients walk more than 30 min/day; however this does not mean that they are physically active because less than 1/4th of their time spent walking can be considered as moderate-intensity activity [72]. It is obvious that COPD patients have a significantly reduced duration, intensity, and counts of daily physical activity when compared with healthy control subjects. The positive effects of pulmonary rehabilitation (PR) such as an increase in peak workload, peak oxygen consumption, and endurance time have been shown in large clinical trials [73]. However, the increased exercise capacity does not mean that the patient is definitely active in daily life. Therefore, the patients have to accept exercise training as a behavior change, although the impact of pulmonary rehabilitation on physical activity is yet to be clearly and consistently defined [73]. Many physicians advise patients who are unable to participate in a structured PR program to walk at least 20 min/day. The benefits of this general advice have not been tested. However, observational studies have concluded significant benefits of physical activity [11]. Gimeno-Santos et al. [74] evaluated the determinants and outcomes of physical activity in COPD patients. Hyperinflation, exercise capacity, dyspnea, previous exacerbations, gas exchange, systemic inflammation, quality of life, and self-efficacy were consistently related to physical activity but were often based on cross-sectional studies and low-quality evidence. As outcomes, COPD exacerbations and mortality are consistently associated with low levels of physical activity based on moderate quality evidence. Physical activity is associated with other outcomes such as dyspnea, health-related quality of life, exercise capacity, and FEV_1 based on cross-sectional studies and low to very low quality evidence. They concluded that physical activity level in COPD is consistently associated with mortality and exacerbations; however, there is poor evidence about the determinants of physical activity, including the impact of treatment.

A joint statement from the ATS/ERS states that pulmonary rehabilitation "should no longer be viewed as a 'last ditch' effort for patients with severe respiratory impairment. Rather, it should be an integral part of the clinical management for all patients with chronic respiratory disease, addressing their functional and/or psychological deficits" [73]. The recent GOLD strategy recommends that all COPD patients should participate in daily physical activity, although recommended levels have not been defined [11]. The recent World Health Organization guidelines for physical activity recommend that all adults should undertake at least 150 min of moderate-intensity aerobic activity per week, such as walking, to maintain a healthy lifestyle. Individuals limited by medical conditions are advised to undertake as much physical activity as their health allows [75].

As a conclusion, physical activity is reduced in COPD patients. This is associated with a higher risk of hospital

admission and an increased risk of mortality and also places COPD patients at a risk of developing comorbidities. A combination of individualized PR programs and pharmacotherapy in conjunction with behavioral modification may be the way forward to help patients adopt a more active lifestyle.

In conclusion, since the last decades, COPD has been increasingly recognized as a major public health problem. Since the introduction of the new international COPD guidelines such as the GOLD 2011 strategy report, growing interest in the pathogenesis and management of COPD patients has led to notable improvements in patient care and quality of life. COPD is a heterogeneous disease with pulmonary and extrapulmonary manifestations. Inflammation is the central pathological feature in the pathogenesis of COPD. Spirometry remains the gold standard diagnostic tool. Pharmacological and non-pharmacological therapy can improve symptoms, quality of life, and exercise capacity, and through their effects on reducing exacerbations, have the potential to modify disease progression. New guidelines aim to reduce the symptoms and prevent future risks in COPD patients by recommending a combined assessment between symptoms, spirometric classification, and future exacerbation risk. Long-acting bronchodilators are the mainstay of pharmacotherapy. Comorbidities should be actively sought and managed in their own right. Smoking cessation is paramount in managing COPD with promotion of physical activity and pulmonary rehabilitation being other key factors in the management. Despite greater awareness of this common preventable disease and major therapeutic advances during this period, the global impact of COPD remains strikingly large.

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