Chronic Obstructive Lung Disease

Subjects: Others

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The concept of early COPD should be understood from the perspective of the longitudinal course of the disease. This represents an earlier point in the course of COPD that does not yet show spirometric airway obstruction or typical clinical manifestations. It should be distinguished from “mild COPD,” which is generally perceived as a cross-sectional-perspective mild spirometric airway obstruction regardless of the point in the course of the disease. However, due to a lack of evidence to identify COPD patients in the early stages of the course of the disease, many groups have used the definition of mild COPD without distinguishing it from early COPD.

Keywords: COPD ; early ; management ; definition ; treatment

1. Diagnostic Tools for Early COPD

As the definition of early COPD was established based on operational and practical considerations and has several limitations, the diagnosis of early COPD must be made by comprehensive measurements in the clinical field. Clinicians should examine exposure to all risk factors related to various lung-function trajectories affected by early life disadvantages and risk factor exposures from utero (Table 1). In addition, several studies have attempted to detect early changes in the airway and lung tissue indirectly using various physiological, radiological, and laboratory tests.

Table 1. Diagnostic tools for early COPD.

Category	Diagnostic Tools	Supplements
Identification of risk factors	**Tobacco smoking**	***In utero*** **Parental smoking** **Second-hand smoke** **Smoking**
	Childhood infection	
	Respiratory diseases (e.g., asthma)	
	Biomass smoke exposure	
	Air pollution	**NO_2, NO_x, PM10, traffic indicators**
	Occupational exposure	
	Genetic factors	**AAT deficiency, cutis laxa, Marfan syndrome, Ehlers-Danlos syndrome**
Physiological tests	**Accelerated FEV1 decline**	**Annual decline >60 mL**
	$FEF_{25–75}$	**Small-airway obstruction**
	Airway hyperresponsiveness	
	RV/TLC	**Lung hyperinflation**
	Cardiopulmonary exercise test	
	DL_{CO}	**Alveolar destruction**
	Lung clearance index	**Heterogeneity of small-airway function**
	Impedance oscillometry	**Airway resistance and capacitance**

Category	Diagnostic Tools	Supplements
Imaging studies	Chest CT	Distinguishing structural deformities Quantification of emphysema TAC Airway wall thickness Radiographically measured RV/TLC
	Parametric Response Mapping (PRM)	Identification of small-airway disease
	Hyperpolarized MRI	Structural and functional abnormality of lung Regional ventilation Alveolar enlargement Gas diffusion
	Gadolinium-enhanced MRI	Early structural change of COPD
Clinical features	Chronic bronchitis symptom	Cough, sputum in 3 months per year (≥2 consecutive years)
	SGRQ score	Health-related QOL
	6 MWT	Exercise function

6 MWT, 6-min walking test; QOL, quality of life; RV/TLC, ratio of residual volume to total lung capacity; SGRQ, St. George's Respiratory Questionnaire; TAC, total airway count.

2. Treatment of Early COPD

The prevalence of early COPD may be underestimated and has been reported to be associated with substantial symptoms, risk of exacerbation, lung-function decline, and a poor health-associated QOL [1][2][3]. Although there is increasing interest in early COPD, there have been only a few studies related to treatment in groups of patients corresponding to the recent definition of early COPD. To gain insight into the best treatment options, we may refer to previous studies with target populations sharing similar characteristics. In this section, we will discuss previous studies investigating the treatment of early COPD, as assessed using various definitions.

Patients at risk of COPD who have not reached the cutoff for airway obstruction in lung-function tests have been classified as having pre-COPD [4]. The identification of patients who will eventually develop clinically significant COPD is important, as the majority of the smoking population show preservation of normal lung function until the end of their lives [5]. Early interventions for prevention or to impede the progression of the disease should be applied in these patients. Cessation of smoking is expected to play the greatest role in prevention or slowing the progression of the disease in both overt COPD and pre-COPD. The classic Fletcher-Peto model has shown that cessation of smoking results in recovery of the normal rate of lung-function decline, versus an accelerated rate before cessation [6]. The results of the Lung Health Study, a multicenter randomized clinical trial in COPD patients with mild-to-moderate airway obstruction, showed that an intensive smoking intervention program significantly halted FEV1 decline in middle-aged smokers [7]. A follow-up study in patients who had actually succeeded in quitting smoking correspondingly showed a favorable outcome in terms of FEV1 improvement in the first year (average of 47 mL), and halving of the rate of FEV1 decline by the 5-year follow-up compared to those who continued to smoke, regardless of smoking quantity, age, baseline lung function, or airway hyperresponsiveness [8]. Furthermore, this intensive smoking intervention resulted in significant improvement in respiratory symptoms and decreased mortality [9][10]. As the rate of FEV1 decline was decreased in quitters compared to sustained smokers regardless of initial airway obstruction, cessation of smoking may prevent the progression of pre-COPD to overt COPD [11][12]. Avoidance of other risk factors, such as indoor/outdoor pollution or occupational exposure, may also be important, as these are often overlooked but important causes of COPD development. Furthermore, influenza or pneumococcal vaccination in high-risk groups may be helpful to avoid acute exacerbation, which causes a substantial decrease in FEV1 even after recovery from the event [2][13]. Pharmacological interventions in pre-COPD patients have yet to be studied. A clinical trial in pre-COPD patients using indacaterol/glycopyrrolate versus placebo is currently underway, and will probably provide some insights for medical intervention in this group (REdefining THerapy in Early COPD for the Pulmonary Trials Cooperative (RETHINC); ClinicalTrials.gov identifier NCT02867761).

3. Treatment of Early-Onset COPD and Mild COPD

Although the recent definition of early COPD by Martinez et al. specifies age <50 years old, there have been few studies in this early-onset COPD group. Subgroup analysis of the Understanding Potential Long Term Impact on Function with Tiotropium (UPLIFT) study in COPD patients ≤50 years old indicated that use of tiotropium improves SGRQ scores, alleviates lung-function decline, and reduces the rate of acute exacerbations [14]. However, these early-onset COPD studies, as with the limitations of the definition itself, involve COPD patients in whom the disease is already advanced at a young age, which should be taken into account when interpreting the results.

On the other hand, the term “early COPD” has been used interchangeably with the term “mild COPD” (GOLD I or I–II) in previous studies. [8][9][15][16][17]. However, as these studies included “early COPD” patients classified only according to disease severity in a cross-sectional view rather than targeting patients in the early phase of the disease from a longitudinal perspective, these studies are limited in that they likely included COPD patients in the late phase of the disease with a slowly progressing clinical course.

Most of the positive results were derived from studies investigating the clinical effects of long-acting bronchodilators. The MISTRAL study group showed that patients receiving tiotropium in both GOLD I–II and GOLD III–IV groups showed significant reductions in annual number of exacerbations compared to the placebo control group [18]. In addition, subgroup analysis of UPLIFT in GOLD II patients demonstrated that use of tiotropium slowed the rate of FEV1 decline, increased SGRQ scores, and extended the time to first exacerbation or time to exacerbation requiring hospitalization compared to the placebo group [19][20][21]. Furthermore, in a study in GOLD I and II patients, Zhou et al. reported higher FEV1 and lower FEV1 decline rates in the tiotropium group compared to the placebo group [15]. Dual bronchodilator therapy, such as umeclidinium/vilanterol, has recently been shown to have beneficial effects on lung function across all severity stages, including GOLD stage II COPD [22].

Another regimen that has shown positive results is inhaled corticosteroid (ICS) plus long-acting β-agonist (LABA), although there have been relatively few studies of this combination. In the TORCH study, the efficacy of salmeterol plus fluticasone propionate (SFC) was examined in various GOLD severity stages [23]. Patients treated with SFC showed a reduction in moderate-to-severe exacerbation and improved SGRQ scores and FEV1 in all severity groups, including GOLD II [23]. Of note, use of SFC reduced mortality in GOLD stage II patients compared to placebo, which was not confirmed for long-acting muscarinic antagonist (LAMA) or ICS monotherapy [19][23][24]. In addition, the SUMMIT investigators studied the effects of fluticasone furoate (FF), vilanterol (VI), and their combination (FF/VI) in GOLD stage II patients and reported that patients treated with FF or FF/VI showed significant benefits with regard to the FEV1 decline rate [25]. In contrast, evidence for ICS monotherapy has been variable and it has even been reported to have harmful effects, and so further validation is required [24][26][27][28]. In addition, other agents, including short-acting muscarinic antagonists [7][9][29], theophylline [30], and *N*-acetylcysteine [31][32], did not show beneficial effects.

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