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REVIEW

Catching "Early" COPD – The Diagnostic Conundrum

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Abstract: Chronic obstructive pulmonary disease (COPD) remains a leading cause of morbidity and mortality worldwide. Despite this, there has been little progress so far in terms of disease-modifying therapies over the last few decades and this is in part due to poor understanding of the definition and mechanisms surrounding early disease before it becomes established and increasingly complex. In this review, the nuances and difficulty in defining early disease in COPD are discussed. There are clear benefits in identifying patients early; however, usually diagnosis is made in the presence of significant lung damage. We consider what can be learned of early disease from COPD studies and highlight the lack of inclusion of young smokers (who may be at risk of COPD) or those with mild disease. We discuss promising clinical measures that are being used in an effort to detect early disease. These include symptom assessment, lung physiology measures and computed tomography (CT) imaging modalities. There is emerging evidence for the role of neutrophils and their proteinases in early COPD. This may form an important biomarker to investigate the pathophysiological processes of early COPD. Given the importance of the early disease, it is recommended that future COPD studies focus on capturing the earliest manifestations of disease, to understand the initiating mechanisms and to identify novel treatment targets.

Keywords: COPD, early, neutrophil, lung function, biomarker

Introduction

Chronic obstructive pulmonary disease (COPD) is a major cause of mortality[1] and places a high burden on clinical and healthcare resources.[2,3] It is widely believed that the disease is precipitated by an abnormal inflammatory response to noxious stimuli, most commonly cigarette smoke. As the disease progresses, multiple pathological and clinical features emerge including but not limited to loss of small airways, chronic bronchitis, mucociliary dysfunction, bacterial colonization and emphysema.

The treatment of COPD is primarily based on bronchodilators and inhaled corticosteroids in varying combinations and these treatments are increased during exacerbations. The only new class of therapeutic agent to emerge over recent decades has been the phosphodiesterase 4 antagonist, roflumilast which is licensed for use in COPD patients with chronic bronchitis. Although this agent improves lung function and reduces exacerbations,[4] there is currently no clinical evidence it alters the natural history of the disease.

The search for new therapeutic agents has been hampered by the complexity of patient phenotypes and that several components of the disease can become self-

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perpetuating, driving inflammation in their own right. These components may or may not influence the initiating pathological processes or physiological progression. For these reasons, studying the earliest stages of the disease has been perceived as critical. This requires identification of individuals at risk exhibiting the earliest changes in symptoms and pathology before the complexities of the clinical phenotypes become manifest. For this review, "early COPD" refers to a prodromal state where people do not yet have spirometrically confirmed airflow obstruction using standard criteria. However, they are on a clear trajectory to meet these criteria, without effective intervention.

Genome-wide associations have proven largely uninformative and the only widely recognized genetic factor to emerge remains alpha-1 antitrypsin deficiency (AATD) which has a clear mechanistic pathway to explain the COPD that emerges and a physiological measurement that precedes the development of COPD (see later). Similarly, biomarker studies have been largely uninformative[5] probably reflecting the complex inflammatory processes related to the clinical phenotypic variations of established disease. To overcome these issues and understand the precise mechanisms that instigate the disease process, it is imperative that we appropriately study the initial phases of the disease and establish an understanding of what we mean by "early disease".

Understanding "Early" vs "Mild" Disease

In other chronic, non-communicable diseases there have been efforts to study early disease to provide biological insight (for example, the BEACON cohort assessing early rheumatoid arthritis).[6] Effective intervention strategies at an early stage, potentially before the disease process becomes irreversible, will not only improve long-term clinical outcomes but also mitigate subsequent health economic impact. This concept has also gained momentum in COPD and there is consensus that we need to understand more clearly how COPD develops at the earliest stages of the disease process.

In the past, the terms "mild" and "early" COPD have been used interchangeably. However, these terms refer to different concepts. The term "mild" is used as an established marker of severity whereas the term "early" refers to the initiation of a process in time. For example, an 80-year old with a 60-pack year smoking history and a forced expiratory volume in 1 second (FEV_1) of approximately 80% predicted with a decreased FEV_1/FVC ratio for the last five years may be classified as having "mild" disease but not necessarily "early" disease as it has likely developed slowly over decades. On the other hand, a 40-year old with the same lung function parameters may have deteriorated from the normal range rapidly and although mild in physiological terms, likely represents a highly active disease process, present for a short period of time.

Longitudinal studies have provided insight into the difficulty in developing a definition for "early disease". Most studies concentrate on the prevalent FEV_1 and its progression as the surrogate for the COPD condition. The rate of change in FEV_1 over time is variable in COPD (and indeed decline in FEV_1 occurs as part of the normal aging process), with observational studies describing FEV_1 decline rates in established disease ranging from 25–79mls/year[7–9] compared to 24–32mls/year in non-smokers without COPD.[10,11] If these decline rates were consistent throughout the disease course, the time it would take for an individual to reach the diagnostic threshold for COPD would vary (as shown in Figure 1).

The ideal patient population to study and those who would benefit most from early interventions would be smokers with excess lung function decline (above that seen with ageing), as demonstrated in trajectory 3 of Figure 1. This is suggestive of highly active disease. However, on initial assessment, it can be difficult to differentiate between smokers with a fast decline in lung function and those with a much slower lung function decline (Trajectory 2) or those with a decline consistent only with age-related changes (Trajectory 1). Based purely on conventional spirometry, this differentiation requires years of longitudinal follow-up. Furthermore, some individuals can have super-normal peak lung function reflective of an FEV_1 starting above 100% predicted and there is often under-diagnosis of disease in this population as they take longer to reach the "COPD spirometric threshold". It is imperative that we move on from conventional spirometry for the detection of at-risk populations. While we currently cannot reliably predict which smokers are more likely to develop COPD (other than in those with confirmed AATD), there is mounting evidence providing some guidance to gain further insight into biomarkers of risk.

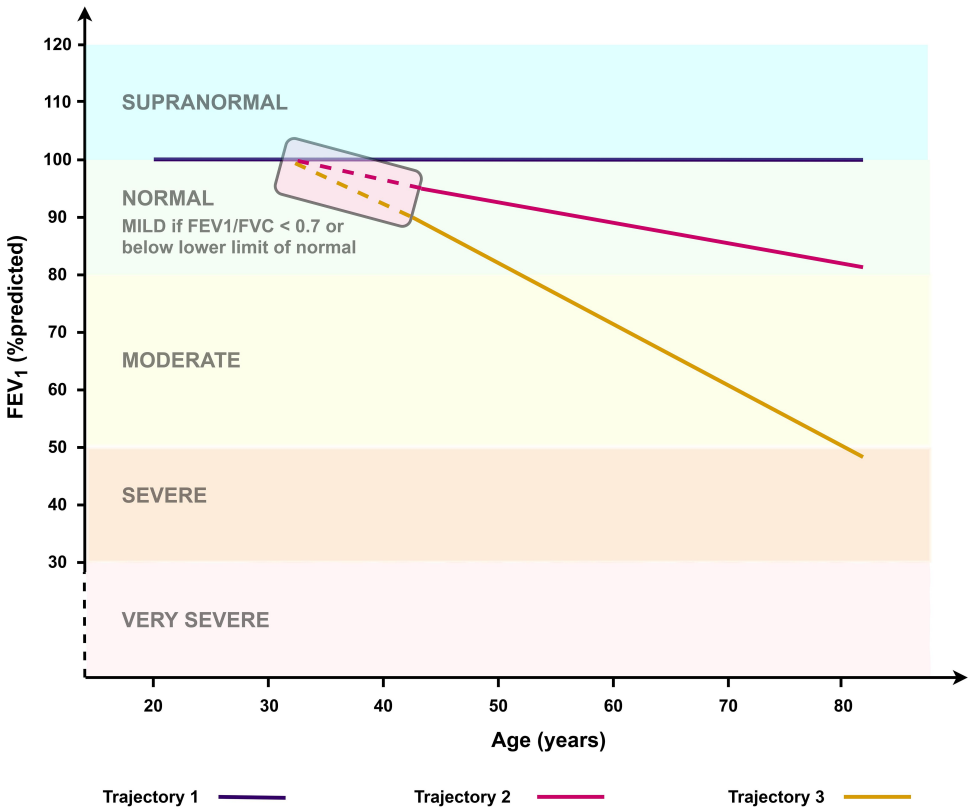

Figure 1 Hypothetical trajectories of lung function (adjusted especially for age but also sex, height and race) that may be seen in the general population of smokers. Horizontal colored areas defined by the vertical axis represent COPD severity according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) staging. Trajectory 1 refers to the lung function trajectory of smokers with decline due to age alone. He/she may not experience any respiratory symptoms or develop COPD. Trajectory 2 represents smokers who have mild decline greater than age-related changes. He/she may eventually cross the COPD diagnostic threshold but may only develop mild disease or respiratory symptoms. Trajectory 3 represents a smoker with an even greater lung function decline and will develop more severe COPD in later life with the associated high morbidity burden. The "early disease" process (represented by the shaded rectangle) is rarely identified and yet should contain the initiating clues to development of COPD especially in those with a more active disease process.

Knowing Where to Look – Pathological Insights

The classical non-proportional Venn diagram of COPD (Figure 2) was first proposed by Snider[12] and was later adopted by the American Thoracic Society.[13] The clinical and pathological features described are major components of COPD and there are currently reliable methods to detect these features. (eg, detection of emphysema by CT scans and airflow obstruction using spirometry). However, these features are reflective of late or moderate to severe disease. Recently studies have concentrated on these phenotypes at all stages of the disease and especially in those with spirometry above the COPD threshold.

In the 1960s, Hogg et al[14] using a retrograde catheter technique, demonstrated that small airway resistance is increased up to 40 times in excised emphysematous lungs compared to healthy human lungs and that this is due to narrowing and destruction of the small airways. Since then, further studies have expanded on this concept. Volumetric CT scanning of participants with varying stages of COPD as well as micro-CT analysis of frozen lung specimens from those with and without COPD have shown that small airways are abnormal or lost even in mild COPD and that this precedes the appearance of emphysema.[15,16] Small airways disease is thus thought to be an early pathological feature of pending COPD and there have been efforts to employ various clinical and diagnostic measures to quantify this in smokers.

Looking for Early Disease (Using the Right Definition)

There is currently a lack of consensus defining "early disease" in COPD but there has been an attempt to define the "at risk" population operationally for research purposes. Martinez et al[17] proposed that early changes leading to COPD should be studied in those younger than 50 years

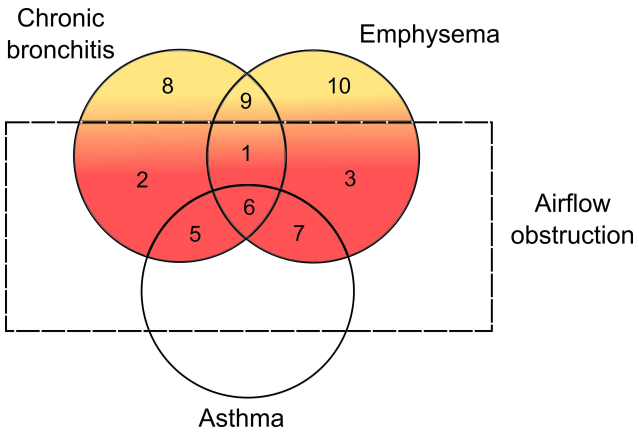

Figure 2 Non-proportional Venn diagram of COPD. This diagram illustrates the subsets of patients with chronic bronchitis, emphysema and asthma. The red areas (subsets 1–7) consist of COPD patients with differing clinical and pathological phenotypes of COPD. The majority of patients with COPD will have airflow obstruction together with features of chronic bronchitis and emphysema (subset 1). Some COPD patients may predominantly have symptoms of chronic bronchitis (subset 2) or emphysema (subset 3) or even have features of asthma (subsets 5–7). Those without airflow obstruction (subsets 8–10) are not classified as having COPD but may have pathophysiological features such as chronic bronchitis (subset 8), emphysema (subset 10) or both (subset 9) that if detected and treated early may prevent progression to established COPD. Adapted with permission of the American Thoracic Society. Copyright © 2021 American Thoracic Society. All rights reserved. American Thoracic Society. Definitions, epidemiology, pathophysiology, diagnosis, and staging. *Am J Respir Crit Care Med.* 1995;152(5pt2):S78–S83. The American Journal of Respiratory and Critical Care Medicine is an official journal of the American Thoracic Society. Readers are encouraged to read the entire article for the correct context at https://www.atsjournals.org/doi/10.1164/ajrccm/152.5_Pt_2.S78. The authors, editors, and The American Thoracic Society are not responsible for errors or omissions in adaptations.[13]

old with ≥10-pack year smoking history with any one of the below:

- early airflow obstruction (post-bronchodilator FEV_1 /FVC less than the lower limit of normal)
- compatible CT abnormalities such as emphysema, air trapping or bronchial thickening
- an accelerated FEV_1 decline (≥60 mls/year) even when in the "normal" range

These criteria need acceptance and validation but represent an important step in moving beyond basic spirometry to identify individuals with high disease activity (and hence a high "inflammatory signal") at a relatively early age. There are currently several studies ongoing using these criteria to identify and assess early COPD including the Early COPD Development Partnership (ClinicalTrials.gov identifier NCT03480347) and the Determinants of Onset and Progression of COPD in Young Adults. (ClinicalTrials.gov identifier NCT02352220) It is hoped that these studies can help elucidate early key pathophysiological processes to predict future COPD.

Looking for Early Disease (Using Common Symptoms)

The use of symptoms to help identify individuals at risk of COPD has been a hotly debated subject over the last few decades. GOLD released a report in 2001 introducing the GOLD 0 stage defined by the presence of risk factors (smoking) and symptoms (chronic cough and phlegm) in the absence of airflow limitation on spirometry. A retrospective analysis of data from the Copenhagen City Heart cohort later showed that GOLD 0 stage was not a stable feature and not all these characterized individuals eventually progress to establish COPD.[18] Because of this study, the GOLD 0 concept was removed from the subsequent 2007 GOLD report.

Although further studies have since supported the dynamic nature of symptoms in smokers, it was suggested that individuals with persistent symptoms have a more pronounced FEV_1 decline[19] and hence greater risk of developing COPD[20] compared to individuals who remain asymptomatic or those whose symptoms resolve. Analysis of data from the National Survey of Health and Development (NSHD) cohort also demonstrated that there was a greater prevalence of chronic bronchitis among smokers between the ages of 36–43 with an associated high risk of incident airflow obstruction in later life.[21] Furthermore, it was shown that the longer the symptoms persist, the faster the FEV_1 declined.[21]

There has thus been compelling evidence for the relationship between the presence of persistent symptoms and subsequent development of COPD. However, there also needs to be a refinement of the term "persistent symptoms" and the potential confounding effects of comorbidities before establishing a clear at-risk population among smokers.

Looking for Early Disease (Using the Right Equipment)

Post bronchodilator spirometry is mandatory for the diagnosis and monitoring of COPD.[22] However, the forced nature of the test means that results are effort dependent and hence subject to intra-patient variability. Standard spirometry assesses flow in the major airways and largely reflects resistance due to narrowing/loss/early closure of

said airways. Hence, they are poor predictors of emphysema[23] and are relatively insensitive to the features of early disease. Thus, it is of limited value unless repeated over several years to identify people on the path to develop COPD through assessment of lung function decline. However, various techniques have been explored to quantify small airways dysfunction as a marker of the early manifestation of COPD. These will be discussed below.

Forced oscillometry technique (FOT) is quick, easy to perform and is obtained during tidal breathing, thus requiring no extra effort from the subject.[23,24] In the ECLIPSE cohort where over 2000 COPD subjects were observed over 3 years,[25] it was shown that peripheral airway resistance (R5-R20), reactance at 5Hz (X5) and area under the reactance curve (Ax) measurements were increased in COPD patients compared to healthy controls and that these measurements were proportionally higher with increasing disease severity.[26] However, attempts to evaluate FOT as a marker of "early" disease in smokers has been limited by the differences of oscillation techniques between studies, small sample sizes and lack of focus on younger smokers where the earliest features of pending COPD are likely to be present.[27] Thus, conformity and longitudinal studies with FOT will be needed before its utility in detecting early disease can be established.

Assessing the forced expiratory loop provides flow measurements that can reflect dynamic airways collapse due to narrowing or weakness of elastic support in the small airways.[23] Maximal mid-expiratory flow (MMEF) quantifies maximal expiratory flow conventionally between 75% and 25% of a forced vital capacity (FVC). It has previously been found that MMEF is significantly lower in GOLD 0 patients and was thus thought to be a marker of early airflow limitation before the diagnostic threshold for COPD is reached by the FEV_1/FVC measurement.[28] Another study supported this concept in two groups of AATD subjects with a normal FEV_1/FVC ratio. Those with a reduced MMEF had noticeably reduced quality of life before emphysema became radiologically apparent and also subsequently showed a faster deterioration in FEV_1 than those without.[29]

Early closure of the small airways has also been assessed by observing gas composition (typically nitrogen) during slow expiration. Such assessments during single-breath washouts are quadriphasic (phase I–IV) and enable the closing volume (CV) of an individual to be quantified.[30] CV is known to be increased in COPD due to premature airway closure but observation of the Phase III slope may be a useful indicator of small airway dysfunction before overt COPD develops.[31] Multiple-breath washouts, on the other hand, enable the lung clearance index (LCI) to be determined.[32] LCI is shown to be a sensitive and repeatable measure of airways disease and can be abnormal before the FEV_1 is significantly impaired.[33] In fact, it is already widely implemented clinically for the identification of early airway pathological features in patients with cystic fibrosis. A recent study has also demonstrated that it may be useful as an indicator of early disease in AATD before abnormal spirometry parameters emerge.[34]

Imaging tools have also been proposed as a method to detect the early disease, as well as identifying the different pathological features of COPD (emphysema, bronchial wall thickening and bronchiectasis). In particular, using CT densitometry to quantify emphysema before it becomes macroscopically obvious may enable understanding of early inflammatory mechanisms of this COPD component whilst these subjects retain normal spirometry.[35] The small airways themselves are impossible to visualize using CT scanning. However, novel imaging techniques such as parametric response mapping (PRM) have been used to assess air trapping independent of emphysema by comparing lung densities at total inspiration and expiration, which likely acts as a surrogate of small airways dysfunction.[36,37] This provides a radiological equivalent of the dynamic airways collapse seen spirometrically.

Apart from the presence of chronic bronchitis and the diagnostic techniques mentioned above, various other concepts have also been explored that may help predict progression to established COPD. Preserved ratio impaired spirometry (PRISm) is defined by a reduced FEV_1 in the setting of a preserved FEV_1/FVC ratio on spirometry. It was found in recent years that patients with PRISm were at high risk of subsequently developing COPD.[38] Due to similar reasons, those with a history of severe childhood asthma[39] and those with evidence of lung airway-parenchymal volume mismatch on CT[40] have also been of particular interest. However, the evidence base surrounding these concepts are currently limited and the clinical utility of such approaches to identify patients at risk or COPD (or indeed when/if these subjects could be classed as early COPD) is unclear.

As demonstrated, there are both physiological and imaging techniques that have shown promise in detecting small airways dysfunction, which likely reflects damage and loss of the small airways seen pathologically in early disease. However, there is currently a lack of robust prospective studies looking at the use of such techniques to identify smokers with subsequent excessive lung function decline (although these are underway). Thus, it remains to be seen whether any of the above might be a more sensitive marker than FEV_1 for the study of the early disease processes in COPD.

The Biomarker Conundrum

Without biological insight, there can be little progress in the development of novel treatments. Furthermore, mapping out early disease mechanisms can help identify molecular biomarkers as well as patient phenotypes that would most likely respond to targeted pharmacological interventions.

In recent years, there has been an extensive array of COPD molecular biomarker study publications. Most of these studies focus on blood biomarkers, instead of lung media, due to ease of access and reproducibility. There are however several issues in the use of such biomarkers in clinical practice and particularly in the field of "early disease". Firstly, although many studies find statistically significant differences in biomarkers between healthy control subjects and COPD patients, there exists marked overlap between individual groups with similarities seen in other non-COPD lung conditions, rendering them ineffective as a prognostic tool.[5] Secondly, there is a - significant day-to-day variability of these markers especially in lung secretions which is unexplained but likely reflects sampling issues. However, such variability can be mitigated to a certain degree by taking sequential samples and using a rolling mean as the result.[40,41]

Thirdly, most biomarker studies focus on COPD populations with the established disease of varying severity and likely varying clinical phenotypes. At this stage, most individuals would already have extensive lung tissue damage with raised levels of inflammatory markers that, at least in part, reflect a physiological response to the damage. It is thus difficult to establish "cause or effect" as the biomarker may simply reflect disease severity rather than disease activity. Thus, biomarker studies in younger smokers with a focus on disease activity before the development of major lung tissue damage coupled with subsequent disease monitoring to assess progression will be needed. This will help identify differences in disease processes in the early stages from those caused by established COPD whilst still reflect future development.

Table 1 illustrates some of the most frequently studied blood biomarkers in patients with COPD. The table does not aim to summarize all studies looking at biomarkers but rather to highlight that such studies tend to focus on the older population (both with and without disease) and patients with a more severe stage of COPD. Therefore, these biomarkers will unlikely be able to capture the key processes in the early disease state and may likely reflect physiological responses to established disease and its severity.

Neutrophil Dysfunction: An Early Signal and a Potential Biomarker?

Over the years many potential mechanisms have been implicated in the pathophysiology of COPD. However, the role of neutrophils and proteolytic enzymes has been widely accepted.[56] Cell and animal studies have demonstrated the ability of neutrophils to damage lung tissues by the release of serine proteinases, such as neutrophil elastase (NE) and proteinase 3.[57] These proteinases degrade all components of the extracellular matrix, leading to the development of emphysema in animal models and (by implication) in humans. These enzymes are also pro-inflammatory in their own right and cause hyperplasia of the submucosal glands and goblet cells, leading to excess mucus secretion and impairment of mucociliary clearance. Subsequently, symptoms of chronic bronchitis and bacterial colonization develop, which further amplifies inflammation.[57,58]

Assays have been developed recently to quantify footprints of lung NE activity systemically by specific cleavage products of lung elastin[59] or the accompanying fibrinogen.[60] Aa-Val^{360} is a NE-specific fibrinogen degradation product reflecting lung elastolytic activity. Plasma levels are raised in stable COPD (especially in AATD) and increase further during exacerbations.[61] Whether the activity levels relate to future outcomes requires further study but the elastin-specific cleavage product does reflect long-term mortality[62] and the fibrinogen footprint does reflect subsequent FEV_1 decline early in subjects with AATD.[63]

There is also an increased understanding of the potential mechanisms of damage caused by dysfunctional neutrophil responses. In the 1980s, it was found that neutrophils from patients with established emphysema had an increased migratory response to chemoattractants

Table 1 Studies of Commonly Researched Blood Biomarkers in COPD with Cohort Demographic Features and Associated Clinical/Physiological Status Together with Outcomes Where These Have Been Documented

Blood Biomarker	Sample Size	Mean Age (Years)	Mean FEV_1 (% Pred)	GOLD Staging	Associations	Ref
CC16	2385	63.4 (COPD) 54.7 (HS) 53.2 (HNS)	48.7 (COPD) 108.6 (HS) 114.8 (HNS)	Stage II – 846 Stage III – 811 Stage IV – 229	Smoking status COPD severity	[42]
	4724	52.1–54.9	N/A	N/A	Smoking status FEV_1 decline	[43]
Fibrinogen	2163	63	48	Stage II – 954 Stage III – 911 Stage IV – 296	Baseline FEV_1 FEV_1 decline	[44]
	5011	72.7	N/A	N/A	Baseline FEV_1 Baseline FEV_1/FVC FEV_1 decline	[45]
sRAGE	295	58.9 (COPD) 52.1 (HS) 56.0 (HNS)	70.4 (COPD) 94.6 (HS) 108.1 (HNS)	N/A	Baseline FEV_1 Baseline FVC FEV_1/FVC decline	[46]
	2759	63.6–66.7 (COPD) 55.0 (HS) 53.8 (HNS)	48.9–49.1 (COPD) 108.4 (HS) 116 (HNS)	Stage II – 1027 Stage III – 989 Stage IV – 241	Emphysema COPD severity	[47]
SP-D	2385	63.4 (COPD) 54.7 (HS) 53.2 (HNS)	48.7 (COPD) 108.6 (HS) 114.8 (HNS)	Stage II – 846 Stage III – 811 Stage IV – 229	Smoking status Exacerbation risk	[48]
CRP	6574	67	80	Stage I/II - 6109 Stage III/IV - 465	Exacerbation risk	[49]
IL-6	2553	63.7 (COPD) 60 (non-COPD)	66.1 (COPD) 99 (non-COPD)	N/A	Baseline FEV_1	[50]
Blood leukocytes	6574	67	80	Stage I/II – 6109 Stage III/IV – 465	Exacerbation risk	[49]
	2138	63	48	Stage II – 945 Stage III – 900 Stage IV – 293	Exacerbation risk	[51]
Blood eosinophils	7428	64–72	50–78	Stage I – 3344 Stage II – 3332 Stage III/IV - 752	Exacerbation risk	[52]
	3448	63.3–68.3	48.0–53.1	Stage II – 1722 Stage III – 1292 Stage IV – 434	Exacerbation risk	[53]
NLR	885	71	53.9–60.8	N/A	Baseline FEV_1 Exacerbation risk	[54]
	664	70.6 (COPD) 68.7 (non-COPD)	58.1 (COPD)	Stage II – 86 Stage III – 124 Stage IV – 158	Mortality Exacerbation risk	[55]

Notes: N/A is listed where data is not available. This is not an exhaustive list and a comprehensive review of all blood biomarkers is outside the scope of this review. Although there is extensive research (previous and ongoing) assessing biomarkers in COPD, most either do not include patients with mild COPD or do not distinguish them from those with more severe COPD. Furthermore, none of the studies include younger smokers (<50 years old) who may be at risk of developing COPD.

Abbreviations: CC16, club cell protein 16; sRAGE, soluble receptor for advanced glycation end products; SP-D, surfactant protein D; CRP, C-reactive protein; IL-6, interleukin 6; NLR, neutrophil-to-lymphocyte ratio; HS, healthy smokers/non-COPD smokers; HNS, healthy non-smokers.

and a more destructive proteinase response than subjects with other neutrophilic lung diseases.[64] This defect of peripheral neutrophils has been confirmed demonstrating migration with increased speed in response to chemoattractants but with reduced accuracy. It was also shown that this was a constitutional defect in COPD patients, with no difference in neutrophil migratory function influenced by COPD severity.[65] Newer research has shown that peripheral neutrophils from smokers with chronic bronchitis but normal lung function have a similar migratory phenotype to those patients with COPD which may influence early pathophysiological changes leading to excess mucus production.[66] However, long-term follow-up is needed to confirm whether this also marks progression to COPD.

These findings taken together could represent an insight into the cause of the early COPD disease process. Neutrophils with dysfunctional migratory dynamics may take a more prolonged and tortuous route towards a chemoattractant source. Thus, as they migrate within the lung architecture, they degrade surrounding lung tissue by creating a trail of obligate neutrophil proteinase activity. This increases bystander tissue damage as the initial high concentration of neutrophil elastase released cannot be inhibited by surrounding protease inhibitors.[67] The exact mechanism affecting the neutrophil response has yet to be elucidated although it is not a secondary response to the environment and can be normalized by specific PI3K inhibitors suggesting this pathway is central.[65,68]

The neutrophil changes discussed above are key mechanisms capable of causing excessive lung tissue damage but individually do not explain susceptibility to COPD. It is becoming clear, however, that a subset of smokers with no spirometric evidence of COPD may already have distinct dysfunctional neutrophil phenotypes.[66] These neutrophils respond abnormally to an inflammatory insult with subsequently increased potential for lung damage and hence would increase susceptibility to developing COPD. This could be genetically determined or reflect epigenetic modifications upon exposure to causative environmental factors.[69]

A prime example of the effect of genetic factors in COPD pathogenesis is AATD. This condition is characterized by low circulating levels of α_1-antitrypsin which normally partially protects lung tissue against damage caused by proteolytic enzymes released from activated and migrating neutrophils. However, although a proportion of AATD patients who are never-smokers develop COPD in middle age, many do not.[70] This observation suggests that aside from an assumed protease-antiprotease imbalance, other epigenetic factors also play a role, even in what is considered a monogenetic condition.

Despite the emerging interest in neutrophil phenotypes, there have been relatively few studies assessing this in-depth in COPD, and none in early COPD. It has been demonstrated by neutrophil proteomic analysis that there exist neutrophil phenotypes that can be functionally different between patients with COPD even if they are not clinically different in terms of symptoms or lung function.[71] Although this study compared neutrophils from healthy subjects and COPD patients, the different stages of COPD severity were not explored. Mapping out these phenotypes in young smokers and assessing whether outliers relate to early disease activity and precede the development of established COPD needs exploration and could provide potential pathways for future therapeutic development.[72]

Why Look for Early COPD?

Identifying individuals with "early COPD" is also important to determine optimal management strategies for this cohort. There have been studies showing that symptomatic smokers have worse quality of life and clinical outcomes compared to "healthy smokers" irrespective of spirometry measurements.[73,74] These individuals are likely to have underlying pathophysiological abnormalities that may require targeted treatment. However, the evidence base surrounding this strategy remains unclear as such patients are not usually included in clinical trials. The RETHINC study is novel as it studies symptomatic current or former smokers with normal lung function on spirometry. This study may provide critical insight into the concept of "early COPD", assessing the impact of dual bronchodilator therapy in this patient population.[75]

Discovery of novel therapeutic agents for "early COPD" (or indeed COPD in general) has also been hampered by the lack of robust biomarkers that are closely linked to the underlying disease mechanism/s. Therapeutic trials that depend on FEV_1 as the traditional surrogate for COPD progression and outcome are expensive as participants require many years of physiological follow-up to determine the disease-modulating effect. Thus, identifying relevant biomarkers would help facilitate short-term Phase II proof of concept studies that would be key to investment in such large phase III studies in COPD (Figure 3).

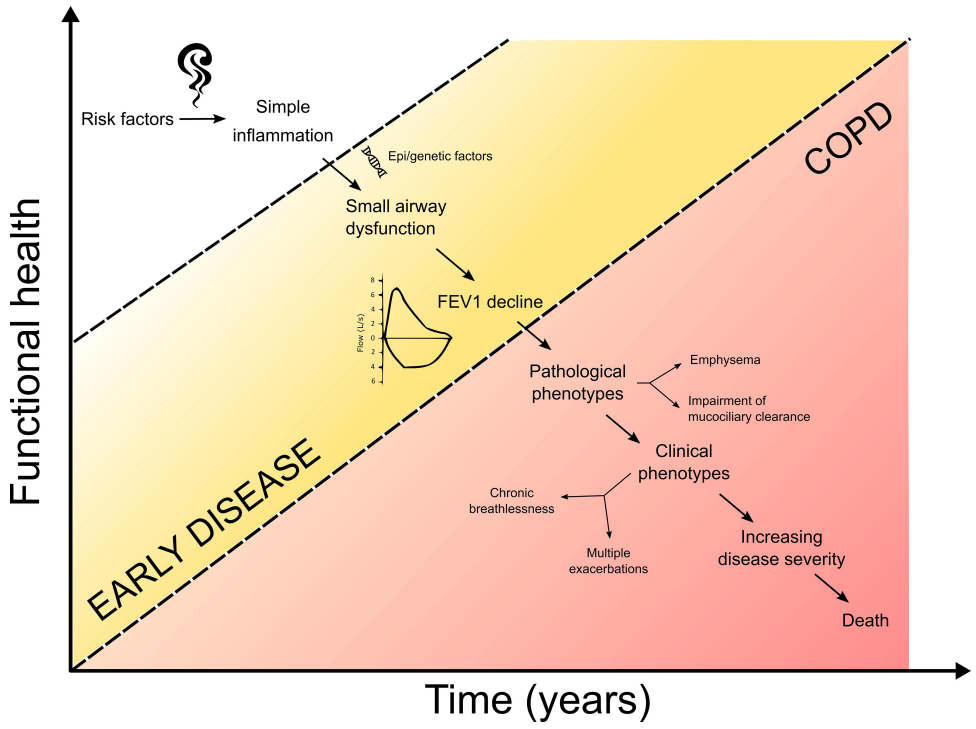

Figure 3 Hypothetical timeline of disease progression in susceptible smokers. Subjects who are persistently exposed to risk factors (eg, cigarette smoke, air pollutants, biomass fuel smoke) suffer from low-grade airway inflammation. However, a subset of them (which may be genetically determined or dependent on epigenetic factors) are predisposed to develop COPD in later life over many years. These subjects may initially develop small airway dysfunction and if highly active, will have rapid lung function decline until they cross the diagnostic threshold for COPD. Many COPD patients are diagnosed only when they suffer from established symptoms and impaired health. At this point, the complexities of the pathological and clinical phenotypes are already established and damage is irreversible which increases the challenge of developing disease-modifying therapies for clinical trials. The most logical approach is to identify disease earlier when the pathological inflammation is only influenced by risk factors and gene/environment susceptibility (white to yellow zone) and not by amplification due to tissue damage and progression to variable phenotypes and their combinations (red zone).

Summary

COPD remains a major non-communicable disease that causes increased morbidity and mortality worldwide. Only 50% of smokers develop COPD, and pathology is likely to progress over many years before the spirometric threshold for diagnosis is passed. To date, the ability to detect patients at risk of progression from early disease to clinically significant disease is limited in clinical practice but remains an important aim in disease prevention and the development of new therapies. This concept remains the most critical target for future COPD research prevention and treatment.

Current therapy (except for smoking cessation) is unable to prevent COPD development or halt its progression once established. Pathological changes are likely irreversible and self-propagating by the time the disease becomes clinically manifest, making it difficult to dissect pathological signals from physiological ones. Neutrophil dysfunction has been studied for many years and is considered central to the development of COPD and its progression. However, it is still unclear if this reflects a response to an abnormal primary factor or whether it is the initiating event in early disease. It is thus important to study younger subjects both at risk of and with the early disease to identify whether this is an early pathophysiological mechanism and hence a novel target for disease modification before it becomes established. Such studies will also help identify biomarkers that reflect causation and predict response to targeted therapies and is crucial for the development of much-needed larger clinical trials.

Disclosure

Professor Robert A Stockley is the investigator lead and reports research funding from Mereobiopharma; reports lecture and travel fees from and chair of Phase 4 advisory board for CSL Behring, member of steering committee for Vertex, chair of Phase 3 Data and Safety Monitoring Board for Kamada, and advisory board for Z factor, during the conduct of the study. Professor Elizabeth Sapey reports grants from HDR-UK, Wellcome Trust, MRC, British Lung Foundation,

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