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EARLY versus MILD Chronic Obstructive Pulmonary Disease (COPD)

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Running Title: Re-establishing stage 0 of COPD.

Key Words: Beginning of COPD, Chronic Bronchitis, Emphysema, airflow limitation, pre-clinical, sub-clinical, clinical, natural history.

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ABRAVIATIONS

ATS = American Thoracic Society

BMI=body mass index

BODE = **B**ody mass index, degree of airflow **O**bstruction, functional **D**yspnea, **E**xercise capacity

CAT = COPD Assessment Test

COPD = Chronic Obstructive Pulmonary Disease

ERS = European Respiratory Society

FEV1 = Forced Expiratory Volume in one second

FVC = Forced Vital Capacity

GOLD = Global Initiative for Chronic Obstructive Lung Disease

HRCT = High Resolution Computed Tomography

mMRC =modified Medical Research Council

6MWD = 6 Minutes Walking Distance

ABSTRACT

Chronic Obstructive Pulmonary Disease (COPD) is very a common, with great morbidity and mortality, disease

Since the beginning of the disease cannot be detected with precision and by using only FEV1 to monitor the evolution of the disease, the Natural History of COPD is rather obscure and sometimes controversial.

Therefore, the terms EARLY COPD and MILD COPD have been used indistinguishably in the medical literature.

In this review we discuss the two terms trying to clarify some of the definition issues, starting with a synopsis of the Natural History of the disease.

We recommend to use the term EARLY COPD for the pre-clinical stage of the disease (stage 0) and the term MILD COPD when the diagnosis is confirmed by spirometry and FEV1 is above 80% predicted. However, COPD is a complex disease and spirometric evaluation alone (MILD COPD, stage I), cannot fully describe the clinical status of the patient.

We conclude that biomarkers to detect the starting point and been able to follow the natural history of the disease more accurately, beyond FEV, are urgently needed.

INTRODUCTION

It is well known that Chronic Obstructive Pulmonary Disease (COPD) is a very common disease with great morbidity and mortality [1-3]. It is defined by the ATS/ERS as “a preventable and treatable disease state characterized by airflow limitation that is not fully reversible. This is usually progressive and associated with abnormal inflammatory response of the lungs to noxious particles and gases primarily, caused by cigarette smoking”[4]

Despite, the tremendous progress that has been made the last decades in the understanding of the pathophysiology of COPD, the natural history of this disease remains practically incomplete [5]

This is probably due to a number of significant unanswered questions such as:

- a. When is the beginning of the disease?
- b. Do we know all the risk factors of the disease?
- c. Is only a single natural history of the disease?
- d. Can we monitor the natural course of COPD only by Lung function tests?
- e. Do we know all the phenotypes or endotypes of this disease?
- f. Do all phenotypes and endotypes of COP D have the same natural history?
- g. Is the natural history of COPD affected by co-morbidities?

As a consequence of the above unknown factors, the terms early COPD and Mild COPD are used indistinguishably in the medical literature. In this review we will first summarize the current knowledge of the Natural History of COPD and then , we will make an effort to clarify the terms EARLY and MILD COPD .Finally , a few recommendations will be proposed.

Natural History of COPD: a synopsis

Since the classical work of Fletcher C and Peto R, the natural history of COPD is based on the rapid decline of the FEV1 of the susceptible individuals compared to the decline in normal subjects. [6,7]

Thereafter, spirometry was introduced into the diagnosis of the disease and the cutoff point of the ratio FEV1/FVC of 0.7 is required to define COPD.(1,4,8) In accordance with the natural history of the FEV1 decline theory of COPD a very important issue is the values of the spirometric indices that people reach at full development of the lungs ,approximately at their age of 20 years.[9]

Recent studies have shown that a number of individuals reach a significant lower value of FVC than the predicted at that age. Lung development and growth are complex processes and can be affected by various conditions such as, maternal smoking. In addition genetic factor(s), premature and low weight at birth, parental

smoking, very early start of smoking habit, early exposure to environmental hazards, and infections during childhood could be risk factors to develop COPD. [9-18]

Therefore, some investigators consider that the development of COPD starts before birth or during childhood and call it a children's disease [13]

However, according to Fletcher and others, it is well known, that the effects of the risk factors on the respiratory system needs decades of continuous exposure before the disease becomes detectable by spirometry [6,7,19]

This so called pre-clinical stage of the disease includes all the molecular and cellular processes that affect the lungs due to the exposure to environmental hazards.. The epithelium of the airways, as the barrier of the human organism to inspired hazards, is the first line of defense that shows the early alteration.[20-23]

It has been shown that the small airways is the site of the first hit and in some individuals this procedure is going towards the alveoli causing Emphysema, but in others it proceeds towards the large airways causing the symptoms of Chronic bronchitis [24-27]

Briefly, cigarette smoking the most common risk factor for COPD, contains a number of very potent oxidative substances. Those substances produce significant oxidative stress on the epithelial and other lung cells, damaging primarily their DNA. This ,we postulate ,is the beginning of the disease, since cells with damaged DNA are recognized as foreign by the defense system and in particular by the dendritic cells.[19,20,28-31]

This information triggers the immune system to produce specific cytotoxic CD8+ lymphocytes in order to destroy the affected epithelial cells [32]. Cells death , apoptosis as well as, afferomatosis are the consequences of the above, initiating the other biological pathways leading to COPD.[33-35] In addition neutrophiles, macrophages and B-lymphocytes take part in these immune cascades leading via inflammatory processes to the early pathological changes of the disease.[35-37}.However, a number of other mechanisms such us, the proteolytic/oxidant imbalance are involved in the pathogenesis of the disease(36,37).Thus, COPD is the result of complex gene-environment interaction in susceptible individuals.

As a result of the pathophysiological changes occurring during this pre-clinical phase of COPD, symptoms appear, such as ,cough and sputum or dyspnea. Those symptoms usually preceded the classical definition of COPD that needs the spirometric clarification of FEV1/FVC <0.7[38]

This pre-clinical stage was defined as stage 0 of COPD, in the first GOLD papers [39] but it disappeared from the subsequent ones [1,40]

Additionally, recent studies showed the importance of symptoms in the Natural history of the disease [41,42]

Figure 1 is a schematic presentation of the natural history of COPD dividing it into a pre-clinical or sub-clinical, and a clinical phase. Although, it is well known that there are a number of courses that individuals could follow to develop COPD we use this simple approach to clarify the differences between Early and Mild COPD.

Recently an integrated model of the natural history of COPD, the EASI model, had been proposed to approach the concept of the "individual natural histories" (43)

A more detailed analysis of the natural history of the disease that is beyond the aim of this paper had been published recently. (44) The authors discuss the gaps and research opportunities of the COPD natural history. They concluded that there is not a single natural History. (44)

Therefore, biomarkers to identify the susceptible individuals (at risk) who may develop COPD, if exposed risk factors, are urgently needed [45,46]

EARLY COPD

The word **early** is a time adjective describing the situation at or very near the beginning of a process and it is commonly used when the starting point of a procedure cannot be defined with accuracy [44,47].

Since, we are not able to know with precision when the COPD begins, this term could be used to denote the pre-clinical phase(s) of the disease.

There is a number of theories postulating the starting point of COPD.

Some scientists consider important the development of the respiratory system, Their proposal is that, since the disease is defined by spirometric parameters (FEV1, FVC), if a person starts his adult life with low values it is more probable to develop the disease when exposed to risk factors compared to a person with higher lung volumes [13,17].

These scientists notice that the pathogenesis of COPD may start very early in life and thus, they consider COPD as a "childhood disease". [13]

However, current literature considers COPD as a disease that primarily begins in adolescence or adult life, when the majority of the patients commence cigarette smoking and unfortunately is detected in mild life. It is well known, that from the time of exposure to risk factors (cigarette smoking) the development of clinical relevant disease, as defined by spirometry, two to three decades are needed.

However, this pre-clinical stage of the disease is very important since it is the time that the molecular and cellular changes occur leading to structural damage of the lung and causes the early symptoms [20-27,38].

A number of molecular alterations, primarily of the DNA of the epithelial cells of the airways, occur due to the exposure to risk factors. Thus, the disease is considered as an epigenetic one, since the environment affects the genome of susceptible individuals at the beginning of the pathophysiological process of the disease [20-23].

Great efforts have been made to discover biomarker(s) in order to identify those susceptible individuals and to detect the disease at a very early stage to avoid the risk factors and thus, to prevent COPD [47,49].

These molecular changes, at the beginning of the disease, cause cellular alterations leading to an “abnormal” or better “enhanced” inflammatory response of the lung.[4]

This inflammatory cascade may be responsible for the early structural changes, seen in the small airways. [50,51]

Narrowing of the airways and / or destruction of the alveoli are the pathological changes responsible for the appearance of the early symptoms, such as, tightness of the chest, cough and sputum, as well as dyspnea on exertion [24-26].

Unfortunately by the time symptoms appear there is a critical loss of lung units [47]. However, as stated earlier, in order for the loss of lung function to become severe and detectable with simple spirometry, decades of exposure are required. Recently, research showed, once more, the importance of the early symptoms in the detection of the individuals at risk to develop COPD [52-58].

In addition to the pulmonary function tests[59], radiographic methods, such as HRCT have been used to identify emphysema at an early stage [60-62] .

Therefore, great effort should be made for the early detection of COPD during its preclinical stage (stage0) and if possible before the early symptoms appear.

Early stage detection makes prevention (smoking cessation) a reasonable and ambitious goal for COPD

The following recommendation may lead to the improvement of the prevention of COPD.

1. Re-establish stage 0 or at risk to develop COPD in the guideline literature.
2. Consideration of the early symptoms (cough / sputum), without the spirometric values of COPD, as pre-clinical stage of the disease.

3. Further, research for biomarkers for early detection of COPD at pre-clinical stage at the molecular level.
4. Improvement of small airways function tests or radiological methods (HRCT) in order to detect early structural changes of the lungs.
5. Universal measurement of spirometry at the age of 18-20 years .

MILD COPD

The word **mild** is an adjective of quality, describing a condition that is not severe or is gentle in nature.

According to the diagnostic criteria any patient with dyspnea, chronic cough and/or sputum and history of exposure to risk factors must be considered as COPD. The common risk factors are tobacco, occupational hazards, indoor/outdoor pollution and the use of biomass.

However, a spirometric evaluation is needed to confirm the diagnosis with the presence of the ratio of FEV1/FVC <0.70 after proper bronchodilation [1,4,8].

Thereafter, the value of FEV1 is used to clarify the severity of the disease:

Table 1 shows the classification of severity of COPD in accordance with the spirometric values of post –bronchodilator FEV1 [4].

Mild COPD is determined by spirometry when FEV1/FVC <0.70 and FEV1 > 80% of the predicted values [1,4].

Even at that stage of the mild disease there are significant structural defects of the lungs. In addition the cellular inflammatory processes are well established in the airways as reported by Hogg et al [24,25]. Moreover, patients at that stage utilize health care resources for COPD [64,65]. In addition it was shown that even this mild by spirometry classified stage, exacerbation of the disease may occur [65].

In addition, the QoL of Mild , by spirometry, COPD patients, could be significantly affected. It is obvious that other clinical parameters are needed to evaluate properly the severity of the disease [66].

The BODE index was one of the first to include other criteria, such as, the BMI, the 6MWT and dyspnea severity index, in the spirometry to evaluate the severity of COPD [67].

The latest GOLD consensus reports, propose, in combination with the spirometric assessment (stage I,II,III,IV), the “ABCD” system, including the symptom of dyspnea and the history of exacerbation, to classify properly the severity of the COPD patients [1].

Therefore, a mild patient by spirometry ($FEV_1 > 80\%$) could be class A, if he has 0 or 1 exacerbation not leading to the hospital and mMRC 0-1 or CAT < 10. He can be B if have the same exacerbation history (0-1) but mMRC > 2 or CAT > 10. A Mild COPD, by spirometric evaluation, could be class C if he has an exacerbation history of > 2 the last year or 1 leading to the hospital and mMRC 0-1 or CAT < 10. Rarely, a Mild COPD patient could be classified as D. Thus, the term Mild that is determined only by spirometry ($FEV_1 > 80\%$) does not reflect the total clinical condition of the patient.

Discussion

Since the classical report of Fletcher and Peto (6,7) spirometry has been used to monitor the Natural History of the disease. Later the spirometric indices were used to define COPD and to evaluate its severity. However, the disease begins a lot sooner than the spirometric index of FEV_1/FVC become less than 0.7 to confirm the diagnosis of COPD [65,66,67].

This pre-clinical period of the disease could be very long and characterized by years of exposure to risk factors, primarily cigarette smoking. During this phase of the disease molecular, cellular, inflammatory and structural changes occur in the lungs. Some of these inflammatory procedures may produce mediators that can spilled over beyond the lungs. [49]

This "silent" phase is followed by the early appearance of symptoms such as, cough sputum and dyspnea. These early symptoms precede by long time, the development of a spirometric defined COPD. [38]

It is well known, that by the time the ratio FEV_1/FVC become than 0.7 a significant part of the functional units of the lungs is destroyed.

Therefore, it is obvious that the pre-clinical, (stage O), EARLY COPD is very important in order to identify the patients at risk and prevent the disease, which is ambitious task for the medical community.

On the other hand, it has been shown that the spirometric MILD COPD, stage I, does not provide accurate evaluation of the of the clinical condition of the patient.

Even, at that Mild stage I, some patients showed significant deterioration of their QoL [64].

They may have exacerbation(s) and severe dyspnea as measured by mMRC scale. [63]

Therefore, efforts have been made to improve the severity scales beyond FEV_1 . Such a successful severity index is the BODE index. Celli et al using FEV_1 , 6MWD, mMRC and BMI developed the BODE index to evaluate the severity of the disease as well as, to predict long-term outcomes and death [67].

Later, the GOLD statements introduced the ABCD severity system, that in the last edition, uses the number and quality of exacerbations, as well as, the evaluation of dyspnea in

order to assess the total state of the disease. Alternative to mMRC score for dyspnea, the CAT score can be used [1].

Thus, it is well accepted that the value of FEV1 alone cannot represent accurately the severity of the clinical condition of a COPD patient. The severity of symptom, the exacerbations, measurement of QoL, other functional parameters such as 6MWD or diffusion capacity may improve the accuracy of those scales. In addition the number and the quality of comorbidities have to be taken in to consideration.[68-70]

Recently radiographic methods have been used to detect the disease early and /or add to the severity evaluation.[59-61]

Therefore, it is recommended to use the term MILD COPD , not only when the FEV1/FVC is <0.7 and the FEV1 $> 80\%$ pred but in combination with the absence of exacerbations, mild dyspnea (mMRC=0-1) and mild reduction in the distance of 6 minute walking test (6MWD).

Finally, the importance of the of the pre-clinical phase of the disease has been noticed and it is recommended to use the term EARLY COPD to define this stage as stage 0.

We strongly believe that the medical community has to re-establish stage 0 in order to increase the awareness of the disease globally and finally to succeed to prevent the disease.

Biomarkers to screen for EARLY COPD are urgently needed.

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LEGENT OF FIGURE

Figure 1: Natural History of COPD divided into pre-clinical(stage 0) and clinical phases (stage I, II,III,IV)

A = The developmental stage of the lungs

B[early]= Exposure to risk factor(s) and initiation of the molecular, cellular, structural changes

B[late]= Early symptoms without spirometric obstruction ($FEV_1/FVC > 0.7$) and possible detection by the Diffusing Capacity, tests of the Small Airways and HRCT.

CI= Mild COPD

CII= Moderate COPD

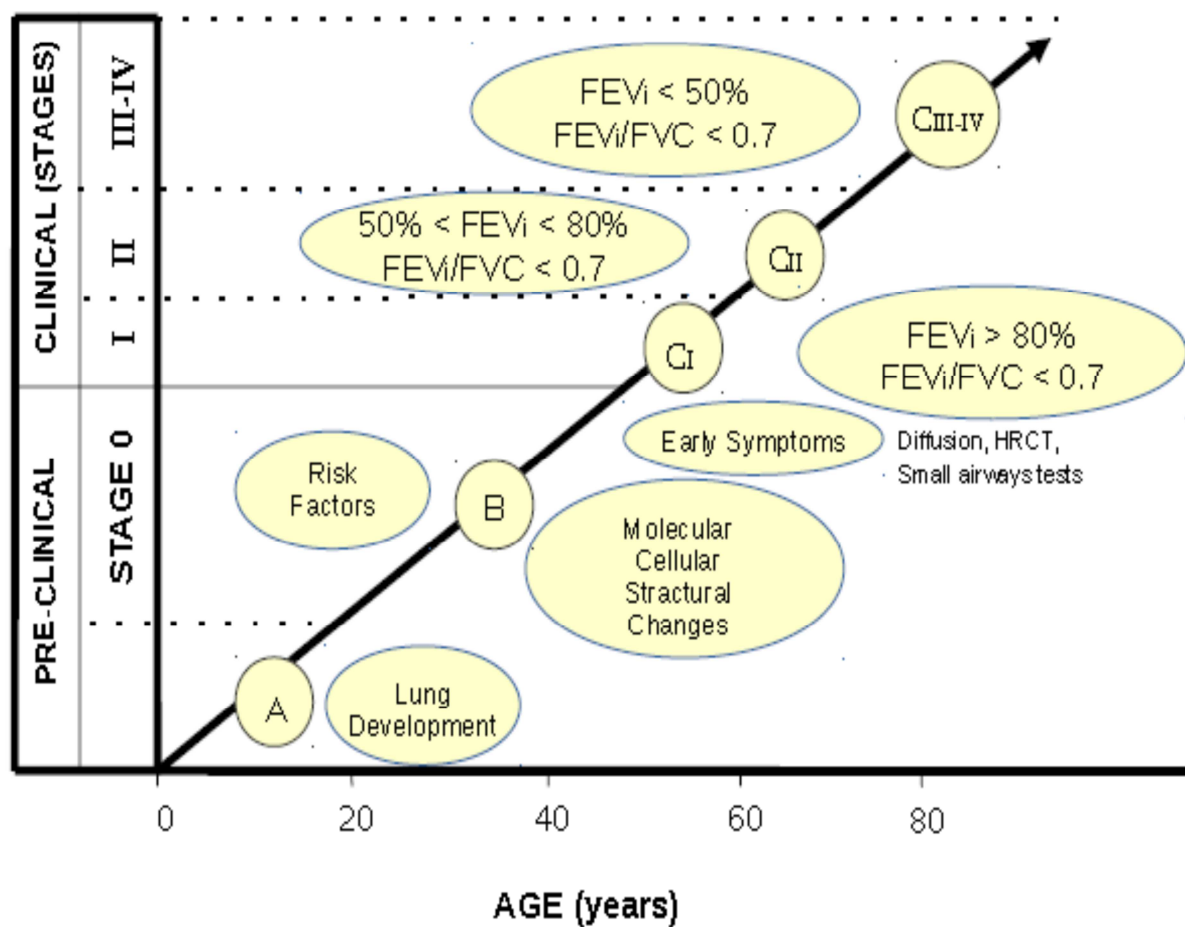
CIII-VI= Severe – very severe COPD

Table 1. Severity of COPD . Based on post-bronchodilator FEV1. ($FEV_1/FVC < 0.7$)

STAGE I	Mild	$FEV_1 \geq 80\%$ predicted
STAGE II	Moderate	$50\% \leq FEV_1 < 80\%$ predicted
STAGE III	Severe	$30\% \leq FEV_1 < 50\%$ predicted
STAGE IV	Very Severe	$FEV_1 < 30\%$ predicted

ACCEPTED MANUSCRIPT

NATURAL HISTORY OF COPD



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