Since the seminal report by Fletcher and Peto, the development and progression of chronic obstructive pulmonary disease (COPD) has been related to an increased rate of lung function (FEV\textsubscript{1}) decline. Recent studies show that not all patients with COPD decline rapidly and that actually, the majority does not. What factors are involved in the path determining the ultimate progression of COPD remains unknown, but it is a subject of intense recent research. Here, we present some very recent observations that may contribute to improving our understanding in this field.

First, a combined analysis of three large and independent cohorts (The Lovelace Smokers Cohort (LSC), The Framingham Offspring Cohort (FOC) and The Copenhagen City Heart Study (CCHS) has addressed the importance of FEV\textsubscript{1} at early adulthood (<40 yrs.) and FEV\textsubscript{1} decline on the occurrence of clinical COPD (GOLD grade ≥2) later in life in ever-smoking adults. The main results showed that about half of the individuals with COPD at the age of 50-65 years, had attained normal FEV\textsubscript{1} before the age of 40 years and experienced a rapid decline of FEV\textsubscript{1} thereafter, whereas the other 50% had a reduced FEV\textsubscript{1} in early adulthood and a subsequent normal FEV\textsubscript{1} decline, despite similar smoking exposure. Among the individuals with an FEV\textsubscript{1} < 80% ref. before the age of 40 years, 26% had COPD after 22 years of observation, whereas the corresponding number among individuals with baseline FEV\textsubscript{1} equal to or above this threshold was 7%. These results indicate that COPD is not always caused by rapid FEV\textsubscript{1} decline and that a low FEV\textsubscript{1} in early adulthood is also an important independent contributor in the genesis of COPD. The challenge now is how to identify these different trajectories in clinical practice and research.

On the other hand, the ECLIPSE study reported a significant inverse association between the rate of FEV\textsubscript{1} decline and serum levels of Clara Cell 16 protein (CC16) in COPD patients, recently confirmed in another cohort of mild COPD patients. Earlier studies showed that low CC16 levels in lung epithelial cells are associated with COPD and that low serum levels of CC16 are independently associated with subsequent development of lung cancer. The Club (formerly Clara) cell protein (CC16 in humans, CC10 in mice, also known as secretoglobin 1A1, club cell secretory protein (CCSP), urotoglobin, and urine protein-1) is a 15.8-kDa homodimeric protein and is secreted by non-ciliated bronchiolar Club cells. It is the most abundant protein present in normal airway secretions and is present in serum. CC16 plays an important role in maintaining homeostasis of the airway epithelium and has anti-inflammatory activity in the lung.

Serum CC16 levels are low in cigarette smokers, and patients with asthma, and obliterative bronchiolitis. Thus, most everyone agrees that CC16 is an important biomarker of risk for rapid FEV\textsubscript{1} decline, but whether it plays a role in the pathogenesis of the disease is not known. We have recently conducted a series of studies in humans and animals that suggest that CC16 is not only a biomarker, but that it also plays an important role in protecting the lung from injury by cigarette smoke. In the LSC there is an association of plasma CC16 levels and FEV\textsubscript{1} decline. The relationship between CC16 level and chronic bronchitis has been evaluated not only in the LSC but also validated in the ECLIPSE cohort. The results show that smokers with reduced plasma CC16 levels are at higher risk for having a faster rate of FEV\textsubscript{1} decline, presenting with COPD, and chronic bronchitis. Furthermore, while all SNPs within the
CC16 gene promoter region analyzed are significantly associated with plasma CC16 levels, two of the 10 SNPs were associated with FEV\textsubscript{1} decline and another one with chronic bronchitis. Whether supplementation of CC16, or its augmentation, may have therapeutic effects for FEV\textsubscript{1} decline and chronic bronchitis remain to be determined.

All in all, the above reviewed recent scientific evidence contributes to improving our knowledge on the natural history of COPD.

**Bibliography**


