[Original Research]

CHEST

Disease Severity Dependence of the Longitudinal Association Between CT Lung Density and Lung Function in Smokers

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BACKGROUND: In smokers, the lung parenchyma is characterized by inflammation and emphysema, processes that can result in local gain and loss of lung tissue. CT measures of lung density might reflect lung tissue changes; however, longitudinal data regarding the effects of CT lung tissue on FEV_1 in smokers with and without COPD are scarce.

METHODS: The 15th percentile of CT lung density was obtained from the scans of 3,390 smokers who completed baseline and 5-year follow-up of the Genetic Epidemiology of COPD (COPDGene) study visits. The longitudinal relationship between total lung capacity-adjusted lung density (TLC-PD15) and FEV_1 was assessed by using multivariable mixed models. Separate models were performed in smokers at risk, smokers with preserved ratio and impaired spirometry (PRISm), and smokers with COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) staging system.

RESULTS: The direction of the relationship between lung density and lung function was GOLD stage dependent. In smokers with PRISm, a 1-g/L decrease in TLC-PD15 was associated with an increase of 2.8 mL FEV_1 ($P = .02$). In contrast, among smokers with GOLD III to IV COPD, a 1-g/L decrease in TLC-PD15 was associated with a decrease of 4.1 mL FEV_1 ($P = .002$).

CONCLUSIONS: A decline in TLC-PD15 was associated with an increase or decrease in FEV_1 depending on disease severity. The associations are GOLD stage specific, and their presence might influence the interpretation of future studies that use CT lung density as an intermediate study end point for a decline in lung function.

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KEY WORDS: CT scan; lung density; smoking

ABBREVIATIONS: AATD = alpha$_1$-antitrypsin deficiency; GOLD = Global Initiative for Chronic Obstructive Lung Disease; ILA = interstitial lung abnormalities; PD15 = 15th percentile of lung density; PRISm = smokers with preserved ratio and impaired spirometry; TLC_{CT} = total lung capacity by CT scan; TLC-PD15 = 15th percentile of lung density adjusted for total lung capacity

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Emphysema is defined as abnormal permanent dilation of the distal airspaces,[1] and numerous investigations have shown that CT imaging is able to provide in vivo assessments of this pathologic process.[2,3] Densitometric measures of the lung parenchyma have been used in clinical, epidemiologic, and genetic investigations, and this research has repeatedly demonstrated the ability of CT densitometry to be a biomarker for disease stratification.[4-6] Subjects with greater amounts of pathologically low attenuating lung tissue on CT imaging have more severe COPD.[7] These cross-sectional data strongly suggest that CT scanning could also be used as an intermediate study end point in which change in lung density is related to loss of lung function. There are few published data, however, supporting that contention.

Although the relationship between changes in CT lung density and lung function has been observed in smokers with alpha$_1$-antitrypsin deficiency (AATD),[8-10] this association has not been convincingly shown in longitudinal observational studies of smokers without AATD.[11-15] This finding may be, in part, due to the relative severity of AATD vs non-AATD parenchymal remodeling but also the complex nature of parenchymal remodeling in smokers. Inflammation might precede centrilobular airspace dilation. When observed Q9 macroscopically using CT imaging, this will effectively result in a local gain and then loss of lung density as the remodeling process evolves from normal tissue to emphysema.

One way to determine the presence of such a phenomenon is to stratify a cohort according to disease severity with the assumption that those with less severe disease are at a different stage of parenchymal remodeling than those with more severe COPD. We therefore sought to determine if longitudinal CT densitometry was related to loss of lung function using data from the Genetic Epidemiology of COPD (COPDGene) study, one of the largest observational investigations in which subjects underwent volumetric CT scanning and detailed clinical assessments at baseline and a 5-year interval follow-up. A priori, we decided to undertake these analyses stratified according to COPD severity to fully leverage the breadth of smoking-related lung disease represented in the COPDGene study cohort.

Methods

Study Population

Q10 The COPDGene study has been described in detail previously[16] and is expanded on in e-Appendix 1. At baseline, subjects underwent detailed characterization, including the following: volumetric inspiratory CT scans of the chest; questionnaires; and spirometric measures of lung function. COPDGene subjects were asked to return for a 5-year interval visit to repeat the characterization performed at baseline. We used the first 5,000 dataset of subjects who completed the second visit for this analysis.

Classification of Smokers

Q11 Based on their spirometric measures (see e-Appendix 1), subjects were then classified as follows: (1) smokers at risk (ie, normal spirometric data): $FEV_1/FVC \geq 0.7$ and FEV_1 % predicted ≥ 80; (2) smokers with preserved ratio and impaired spirometry (PRISm)[17]: $FEV_1/FVC \geq 0.7$ and FEV_1 % predicted < 80; and (3) smokers with COPD: $FEV_1/FVC < 0.7$. COPD severity was further classified into Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages I through IV.[18,19] GOLD III and IV were combined because of smaller sample sizes.

Clinical Assessment

Subjects' demographic and clinical data (including smoking history, history of congestive heart failure, and acute respiratory disease events[20]) were obtained with standardized questionnaires (available at www.COPDGene.org). More details on this topic are available in e-Appendix 1.

CT Assessment

Volumetric inspiratory CT scans of the chest were acquired at maximal inflation according to standardized coaching and practiced breath-holding.[16] Baseline and follow-up inspiratory CT scans were used in this analysis. Details on CT protocols, visual assessment for interstitial lung abnormalities (ILA), and lung density measurements are provided in e-Appendix 1. Briefly, on baseline CT scans, ILA and interstitial lung disease were identified as previously described.[21,22] We used the lung density at 15th percentile (PD15) of the Hounsfield unit distribution adjusted for predicted total lung capacity (TLC) (measured by using CT imaging) on baseline and follow-up scans (hereafter referred to as TLC-PD15) as the main CT measure.[12]

Statistical Analysis

More details on statistical analysis are described in e-Appendix 1. Multivariable linear mixed models were used to assess the longitudinal relationship between the FEV_1 and TLC-PD15. The

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