[Original Research]

CHEST

Collagen Degradation and Formation Are Elevated in Exacerbated COPD Compared With Stable Disease

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BACKGROUND: The role of the extracellular matrix (ECM) structure and remodeling thereof in lung diseases is gaining importance. Pathology-related changes in ECM turnover may result in deleterious changes in lung architecture, leading to disease in the small airways. Here, degradation fragments of type I (C1M), type IV (α1 chain, C4M2), and type IV (α3 chain, C4Ma3) collagen, all degraded by metalloproteinases and the pro-form of collagen type V (PRO-C5) were investigated and associated with COPD severity and outcome.

METHODS: In a prospective, observational, multicenter study including 498 patients with COPD Gold Initiative for Chronic Obstructive Lung Disease stage 2 to 4, ECM markers were assessed in serum at stable state, exacerbation, and at follow-up 4 weeks after exacerbation.

RESULTS: At stable state, there was a significant inverse association between FEV_1 % predicted and C1M, C4Ma3, and Pro-C5. C1M, C4M2, C4Ma3, and Pro-C5 were associated with BMI, airflow obstruction, dyspnea, and exercise capacity (BODE) index and the modified Medical Research Council (MMRC) score. C1M, C4M2, C4Ma3, and Pro-C5 were significantly increased from stable state to exacerbation and decreased at follow-up. Furthermore, the biomarkers were significantly higher during severe exacerbation compared with moderate exacerbation. Multivariate analysis adjusted for BMI, MMRC score, unadjusted Charlson score, and FEV_1 %predicted showed a significant influence of C1M, C4Ma3, and C4M2 on time to exacerbation. None of the biomarkers were predictors for mortality.

CONCLUSIONS: Serologically assessed collagen remodeling appears to play a significant role in COPD severity (airflow limitation, dyspnea) and disease outcome (time to exacerbation and prognosis as assessed by the BODE index). CHEST 2018; ■(■):■-■

KEY WORDS: basement membrane; C1; C4; COPD; collagen; ECM; cell turnover; lamina reticularis; type I collagen; type IV collagen

ABBREVIATIONS: 6MWT = 6-min walk test; ADM = adrenomedullin; BODE = BMI, airflow obstruction, dyspnea, and exercise capacity; C1M = type I collagen; C4M2 = type IV alpha-1 chain; C4Ma3 = type IV alpha-3 chain; ECM = extracellular matrix; GOLD = Gold Initiative for Chronic Obstructive Lung Disease; MMP = metalloproteinase; MMRC = modified Medical Research Council; Pro-C5 = type V collagen pro-form

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COPD is characterized by various conditions that result in airflow limitation and an abnormal inflammatory response of the lung.[1] Inflammation contributes to airflow limitation by causing excessive remodeling of the airway wall.[2] Lung extracellular matrix consists of cartilage, provisional matrix, a basement membrane, and interstitium.[3] The basement membrane is derived mainly from type IV collagen, which forms the most abundant nonfibrillar collagen in the lung.[3] The alpha-3 chain of type IV collagen is specific to lung and kidney tissue. It plays an important role in cellular proliferation, adhesion, migration, and differentiation. Collagen types I and V are fibrillar collagens. Fibrillar collagens allow the lung to maintain its shape during inflation and deflation and form 15% to 20% of the dry weight of the lung.[3] Collagen types I and V are two of the collagens forming the lamina reticularis, which is a thin layer below the basement membrane.[4,5] Thickening of the lamina reticularis leads to decreased airway distensibility and thus increased airway limitation.[6] Collagen type V is an autoantigen that plays a role in lung transplant rejection and has been shown to correlate to fibrosis. Immunotherapy with collagen type V in patients with interstitial pulmonary fibrosis resulted in stabilized FVC[7]; in animals, it resulted in a reduction in lung inflammation and lung fibrosis.[8]

We and others have previously demonstrated that collagen degradation is up-regulated in patients with COPD[9,10] and is associated with some clinically relevant outcomes of COPD.[11-13] Sand et al[9] showed that the degradation fragments of collagen types III, IV, and VI are increased during exacerbation of COPD compared with follow-up after the exacerbation, but found no association between these factors and disease severity. Degradation fragments of collagen type I and the formation fragments of collagen type VI are inversely associated with FEV_1.[14] Collagen type I degradation is associated with increased mortality in patients with interstitial pulmonary fibrosis[15] and in patients with COPD.[12] Thus far, no data exist regarding the longitudinal expression of the degradation fragments of collagen types I and IV and the formation fragment of collagen type V in COPD stable state, exacerbation, and follow-up. We hypothesize that these particular collagens are associated with disease severity and outcome in COPD.

Methods

Study Design and Patients

Patients in stable state COPD with Gold Initiative for Chronic Obstructive Lung Disease (GOLD) 2 to 4 were enrolled in the Predicting Outcome Using Systemic Markers in Severe Exacerbations of Chronic Obstructive Pulmonary Disease multicenter trial; an observational prospective trial performed in 11 centers in 8 European countries. The study details have been published previously.[11] The study was investigator-initiated and driven and carried out according to the Declaration of Helsinki and Good Clinical Practice guidelines. The institutional review board approved the study (EKBB295/07) and it was registered at www.controlled-trials.com (identifier ISRCTN99586989).

Patients were followed for at least 2 years at scheduled half-yearly visits. All participating patients had a baseline examination at stable state and were monitored for recurrent moderate (requiring treatment with systemic corticosteroids, antibiotics, or both) and severe (requiring hospitalization or a visit to the ED) exacerbations. A follow-up visit was performed 4 weeks after the onset of exacerbation. Clinical history, physical examination, lung function, and the 6-min walk test (6MWT) were performed, and the patients completed the Modified Medical Research Council Score (MMRC), the St. George's respiratory questionnaire COPD version, and the 36-item Short-Form health survey. The latter is a health-related quality of life questionnaire. The evaluation of biomarkers associated with the outcome of the disease was a predetermined end point of the study.

Determination of Biomarkers

Serum levels of fragments of collagen type I (C1M), collagen type 4 (α1 chain C4M2 and α3 chain C4Ma3), and the pro-form of collagen type V (Pro-C5) were measured with Nordic Bioscience assays according to the manufacturer's instructions.[11,15] All assays used a competitive setup with monoclonal antibodies directed against either a protein fragment produced by the metalloprotease cleavage during degradation or formation, or an internal protein sequence as described previously.[15] This means that the assay assesses collagen fragments in which either the N- or C-terminal end is known (depending on the assay); therefore, not only one molecular size is measured, because the length varies depending on how far upstream or downstream from this site it goes. Various fragment lengths were formed depending on how far up- or downstream from the N- or C-terminal was measured.[10,16] A western blot would most likely show a smear of different lengths detected by the antibody. This is a strength of the assay because the assay is not limited to detecting only one fragment, which may be undetectable because of low concentrations. The choice of the fragments to be assessed was made

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