Proteolytic imbalance in COPD
Epidemiological and clinical aspects

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Akademisk avhandling

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Abstract

Aims: 1) To evaluate proteolytic markers in COPD and non-COPD. 2) To study the relationship between proteolytic markers and both lung function decline and prognosis. 3) To recruit subjects from a longitudinal study to a clinical study of disease mechanisms. 4) To study proteolytic markers in airways and serum and their relation to rate of decline in lung function. Methods: Spirometry, serum matrix metalloproteinase-9 (MMP-9), and tissue inhibitor of metalloproteinase-1 (TIMP-1) were evaluated in a population-based study comprising 993 COPD subjects and 993 age- and sex-matched non-COPD referents. Data from 2005 to 2010 were surveyed comprising longitudinal spirometry data and mortality records. For a clinical study, we described the recruitment process of COPD subjects with a FEV₁ ratio of ≤0.60 or ≥0.30 mL/year, along with ever- and never-smoking controls with normal lung function. MMP-9, MMP-12, and TIMP-1 data from bronchial wash (BW), bronchoalveolar lavage (BAL) and serum (collected from 2012 to 2014) were assessed in the clinical study. Results: COPD subjects presented higher serum concentrations of MMP-9 compared to non-COPD subjects (p = 0.017). MMP-9 and MMP-9/TIMP-1 ratio had a negative linear association with the forced expiratory volume in one second (FEV₁) percentage predicted in COPD. Associating the 2005 levels of MMP-9 and MMP-9/TIMP-1 ratio to decline in FEV₁ and FEV₁% predicted, revealed a similar negative association pattern in both non-COPD and COPD, however, this was only significant for non-COPD. A non-response analysis comparing proteolytic marker values from 2005 between participating and non-participating subjects at follow-up in 2010 (excluding deceased individuals) demonstrated significantly higher MMP-9 and MMP-9/TIMP-1 ratios in both non-COPD and COPD, and significantly lower TIMP-1 concentration in non-participants compared to participants. Among the deceased, MMP-9 levels and MMP-9/TIMP-1 ratios were higher in COPD compared to non-COPD. In the longitudinal study, all-cause mortality was higher in the COPD group (16%), than in the non-COPD (10%) (p = 0.008). For the clinical study, 15 subjects were recruited to the two normal lung function groups, while this goal was unachieved for the two COPD groups. The most prevalent reasons for exclusion in the COPD groups were comorbidities. BW- and BAL-MMP-12 concentrations were higher in the COPD group comprising current- and ex-smokers, compared to both ever-smokers (BW: p = 0.001, BAL: p = 0.001) and non-smokers with normal lung function (BW: p = 0.001, BAL: p = 0.001). To evaluate the impact of smoking, COPD ex-smokers were compared to COPD current smokers, with no significant difference in BW- and BAL-MMP-12. In contrast COPD-ex smokers had higher BW- and BAL-MMP-12 compared to ex-smokers with normal lung function, thus suggesting increased BW- and BAL-MMP-12 as markers of COPD rather than of smoking. MMP-12 concentrations in serum were higher for COPD current smokers compared to COPD ex-smokers (p = 0.028), but there was no significant difference between COPD ex-smokers and ex-smokers with normal lung function. BAL-MMP-12 in COPD was associated with annual decline in FEV₁ (r = 0.61, p = 0.005). Conclusion: Extrapolating the data on MMP-9 and MMP-9/TIMP-1 ratio suggest increased proteolytic activity is related to airflow limitation and consequently to COPD severity. Considering the population-based nature of the study, the association of both MMP-9 and MMP-9/TIMP-1 ratio in COPD to mortality risk could be translated to the general population. Increased airway levels of MMP-12 indicated a state of increased proteolytic activity and were associated with rapid lung function decline in COPD. These findings imply that proteolytic imbalance is related to symptoms, lung function decline and prognosis, suggesting it represents a relevant disease mechanism in COPD.

Keywords
Matrix metalloproteinases, MMP-9, MMP-12, lung function decline, epidemiology, COPD, OLIN, KOLIN

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