Biomarkers of collagen turnover and immune cell activity distinguish fibrotic hypersensitivity pneumonitis from idiopathic pulmonary fibrosis

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Background

Idiopathic pulmonary fibrosis (IPF) is the most common cause of pulmonary fibrosis (PF), although it is also present in other interstitial lung diseases (ILDs). Among those is hypersensitivity pneumonitis (HP), an inflammatory disease caused by an exacerbated response to environmental antigens. HP can be classified into fibrotic (fHP) or non-fibrotic (non-fHP). IPF and progressive fHP have similar treatment strategies; however, unlike IPF, HP involves a causal antigen whose removal is crucial. Treatment timing also differs, as HP therapy is usually initiated upon disease progression, whereas IPF treatment begins at diagnosis. Therefore, tools are needed to aid the distinction between fHP and IPF. In IPF, fibrosis is driven by dysregulated wound healing and fibroblast activation, following epithelial injury. In contrast, fHP is characterized by immune cell activation, including T-cells, neutrophils, and macrophages, which, in turn, trigger ECM remodeling and a fibrotic response. All these remodeling processes will lead to the release of protein fragments into circulation. and may serve as biomarkers of disease.

This study aimed to assess tissue remodeling and immune cell activity biomarkers as potential tools to distinguish between HP phenotypes and IPF.

Methods

Biomarkers reflecting ECM remodeling or immune cell activity were measured by specific Enzyme-Linked Immunosorbent Assays (ELISA) in the serum of non-fHP (n=25) and fHP (n=24) patients from the PFBIO-HP cohort (NCT05549635, Hellerup, Denmark) and IPF (n=46) patients from the PFBIO cohort (NCT02755441, Hellerup and Aarhus, Denmark). Data were analyzed with the Kruskal-Wallis test, followed by Dunn's multiple comparisons.

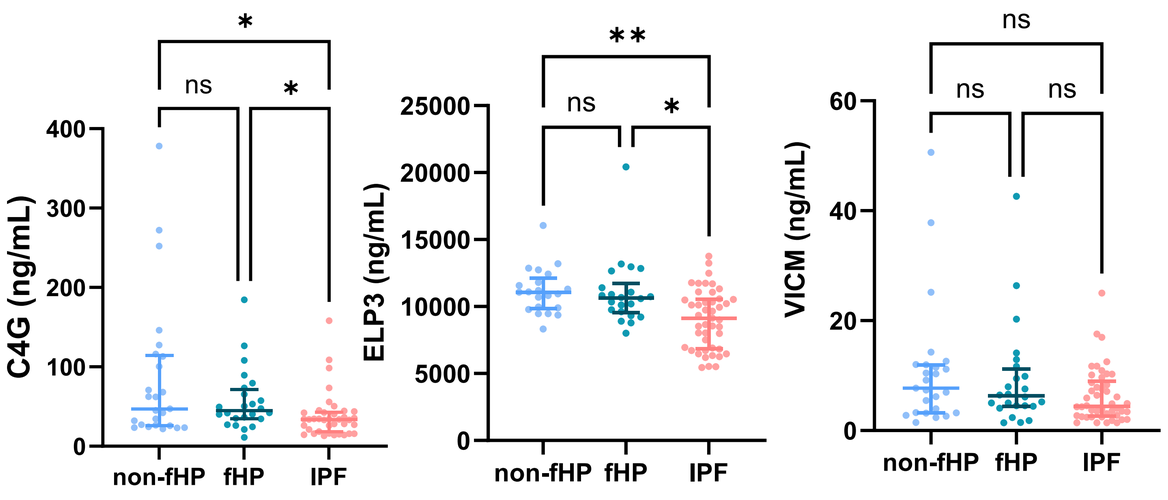
Biomarker	Neo-epitope	Biological process
nordicPRO-C3™	N-terminal pro-peptide of type III collagen	Fibroblast activity
nordicPRO-C6™	C-terminal of type VIa3 collagen/endotrophin	Fibroblast activity
nordicC3M™	MMP-mediated degradation of type III collagen	Interstitial damage
nordicC6M™	MMP-mediated degradation of type VI collagen	Interstitial damage
nordicC4G™	Granzyme-B-mediated degradation of type IV collagen	T-cell activity
nordicVICM™	MMP-mediated degradation of citrullinated vimentin	Macrophage activity
nordicELP-3™	Proteinase-3-mediated elastin degradation	Elastin destruction/ Neutrophil activity

Baseline Demographics

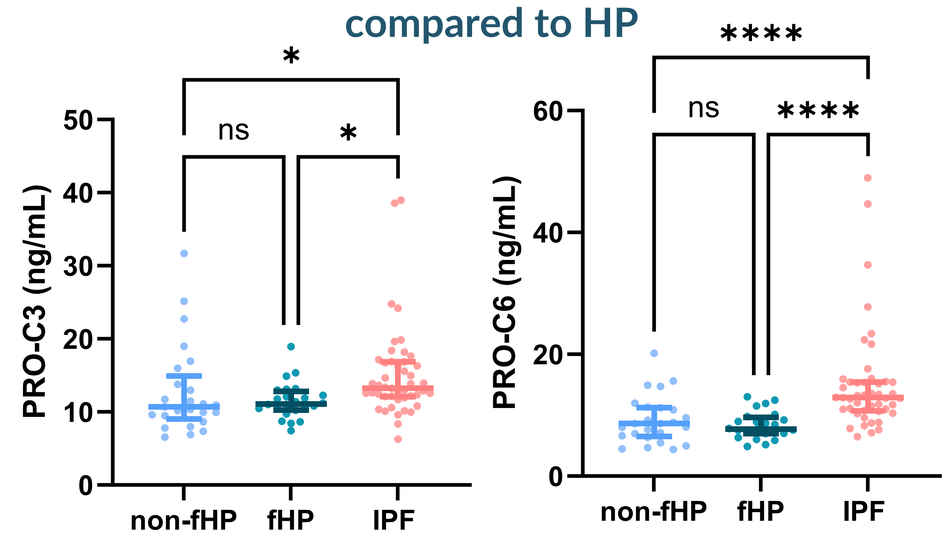
	non-fHP (n=25)	fHP (n=24)	IPF (n=46)	P-value
Age	61.68 (12.40)	64.29 (9.45)	74.28 (7.91)	**< 0.001**
Sex (Male)	8 (32.0%)	15 (62.5%)	34 (73.9%)	**0.003**
Smoking Status (Former)	17 (68.0%)	13 (54.2%)	34 (75.6%)	0.185
BMI, (kg/m2)	28.82 (5.91)	27.23 (4.96)	27.07 (5.04)	0.306
FVC, % predicted	102.30 (19.54)	80.71 (21.26)	88.15 (19.85)	**0.005**
DLCO, % predicted	59.83 (14.90)	51.36 (14.98)	49.48 (13.55)	**0.018**
6MWD (m)	479.25 (170.69)	485.43 (52.09)	420.38 (125.79)	0.332

Data are shown as mean (SD) or n (%). BMI, body mass index; FVC, forced vital capacity; DLCO, diffusion capacity of the lungs for carbon monoxide; 6MWD, 6-minute walk distance; CFB, change from baseline; non-fHP, non-fibrotic hypersensitivity pneumonitis; fHP, fibrotic hypersensitivity pneumonitis; IPF, idiopathic pulmonary fibrosis; SD, standard deviation

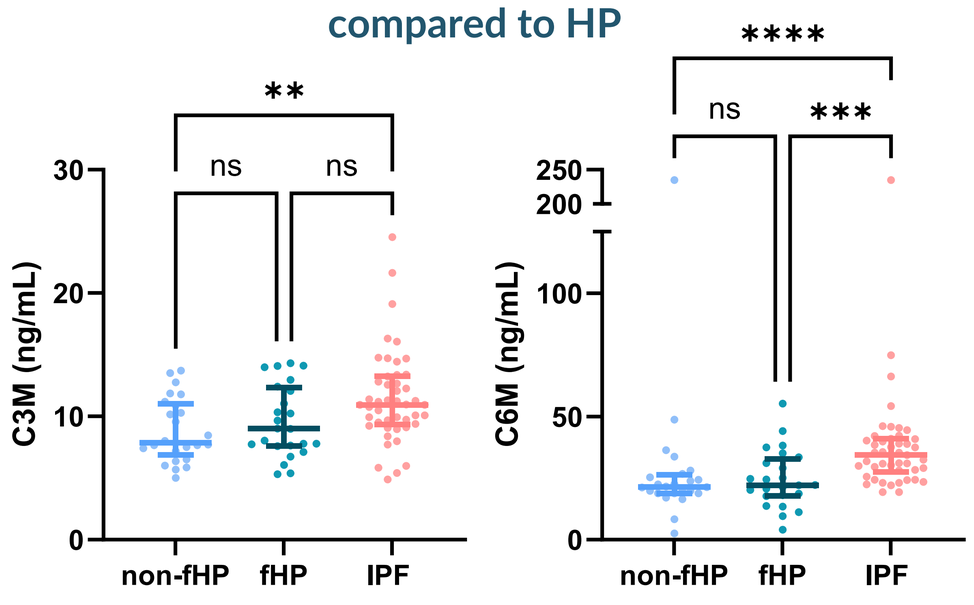
Immune cell activity biomarkers are elevated in HP compared to IPF



Type III and VI collagen formation is elevated in IPF compared to HP



Type III and VI collagen degradation is elevated in IPF compared to HP



Take-home message

Our findings are reflective of the different pathophysiological characteristics underlying each disease and highlights the potential of non-invasive serological biomarkers collagen and immune cell activity as potential tools to distinguish between HP and IPF in the clinic.

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Disclosures: DJL, MAK, JMS and FBS are employees and DJL, MAK and JMS are shareholders of Nordic Bioscience.