Markers of extracellular matrix remodeling and wound healing are associated with fibrostenotic Crohn Disease

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BACKGROUND

Crohn's disease (CD) is a chronic inflammatory condition of the gastrointestinal tract, characterized by excessive extracellular matrix (ECM) remodeling that leads to fibrosis and stricture formation. Strictures are primarily detected using imaging techniques, such as computed tomography and magnetic resonance imaging. However, no validated biomarkers are currently available to assess the presence of strictures. The discovery of such biomarkers would improve early diagnosis and facilitate more effective patient management using anti-fibrotic and anti-inflammatory treatments.

In the current study, we aimed to investigate the association of biomarkers reflecting ECM remodeling, fibroblast activity, and neutrophil activity with CD phenotypes.

METHODS

The cohort included 41 controls (CTR) without a family history of CD or resections, and 129 CD patients divided into four phenotypes: stricture (S) (n=41), inflammation no stricture (I) (n=32), no active inflammation no stricture (NI) (n=46), and stricture with penetrating disease (S/IP) (n=10). Serum markers of collagen type VI formation (PRO-C6), type III and type VII degradation (C3M, C7M), and a human neutrophil elastase-derived fragment of calprotectin (CPa9-HNE) were measured using ELISA. Patients were grouped based on phenotypes, and biomarkers were evaluated by one-way ANOVA, correcting for multiple comparisons using Dunn's test. For two-group comparisons, Mann-Whitney test was applied. The receiver operating characteristic curve (ROC) analysis was performed and the area under the curve (AUC) reported. The global stricture score includes both inflammatory and non-inflammatory components.

RESULTS

C3M, CPa9-HNE, and PRO-C6 showed moderate to significant elevation in CD compared to CTR (C3M: p=0.01; CPa9-HNE: p=0.05; PRO-C6: p=0.07). In patients with CD, PRO-C6 was higher in stricturing than in non-inflamed CD (p=0.04), and CPa9-HNE, C7M, and C3M/PRO-C3 were higher in stricture with penetrating CD than in non-inflamed CD (CPa9-HNE: p =0.02, C7M: p =0.02, C3M/PRO-C3: p =0.009) (Fig. 1). Levels of CPa9-HNE, C3M, and C7M positively correlated with global stricture severity score, and along with PRO-C6, differed moderately to significantly between the upper and lower quartiles of this score (CPa9-HNE: p=0.03, C3M: p=0.03, C7M: p=0.001, PRO-C6: p =0.06) (Fig. 2). ROC analyses show that PRO-C6, CPa9-HNE, C7M and C3M/PRO-C3 have moderate to good discriminative power in distinguishing between disease phenotypes (non active inflammation versus structuring with or without penetrating disease) and between patients with low and high stricuture severity (Fig.3).

Fig.1

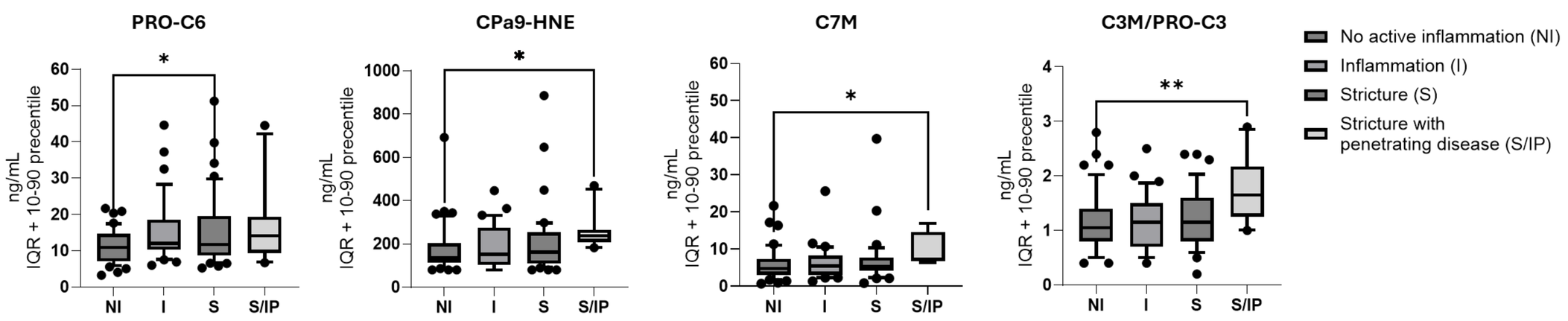

***Fig.1**: Levels of PRO-C6, CPa9-HNE, C7M and C3M/PRO-C3 divided by phenotypes (non active inflammation, inflammation, stricturing, stricturing with penetrating disease). Boxes represent the interquartile range + 10-90 percentile.*

Fig.2

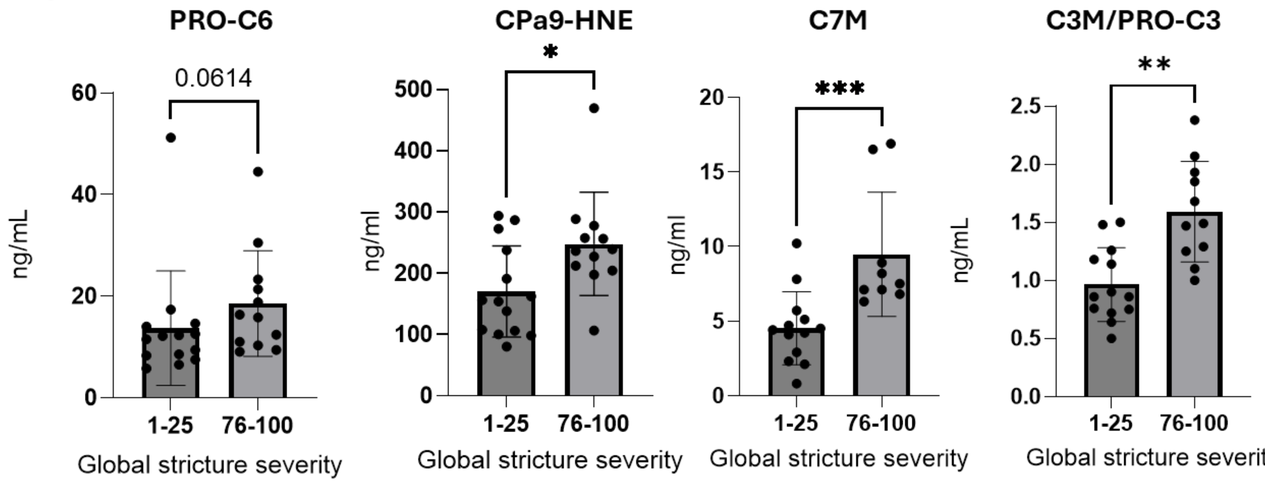

***Fig.2**: Levels of PRO-C6, CPa9-HNE, C7M and C3M/PRO-C3 divided by lowest (1-25) and highest (76-100) global stricture severity. The global stricture severity was determined on a scale from 1-100, with 1 being the mildest stricture and 100 being the worst stricture without a fistula or abscess.*

Fig.3

Phenotype		
BIOMARKER	AUC	P-VALUE
PRO-C6	0.61	0.063
CPa9-HNE	0.83	0.001
C7M	0.80	0.0064
C3M/PRO-C3	0.78	0.006
Global stricture severity		
BIOMARKER	AUC	P-VALUE
PRO-C6	0.72	0.061
CPa9-HNE	0.75	0.03
C7M	0.80	0.0064
C3M/PRO-C3	0.78	0.006

***Fig.3:** ROC analyses showing the area under the curve (AUC) and P-Value for the different biomarkers.*

* p<0.05 ; ** p<0.01; *** p<0.001; **** p<0.0001

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Disclosures: LESA, MARA, TKA, ACBJ, JHM, MK are employed at Nordic Bioscience and may be shareholders

CONCLUSION

The fibrosis marker (PRO-C6) was associated with stenosis and was elevated in CD patients with high levels of global stricture scores. Markers of mucosal damage (C7M, C3M/PROC3) and inflammation (CPa9-HNE) were associated with patients with stenosis and penetrating disease and showed a positive association with the global stricture score. These data suggest that markers of ECM remodeling could be valuable tools for assessing fibrostenosis in patients with CD.