MP414

FIBROBLAST ACTIVATION PROTEIN (FAP)-CLEAVED TYPE III COLLAGEN [C3F] IS A POTENTIAL MARKER FOR INTESTINAL FIBROSIS IN PATIENTS WITH CROHN'S DISEASE

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1) BACKGROUND

- Crohn 's disease (CD) is characterized by chronic inflammation in the gut, where severe complications such as fibrotic strictures require surgical resection.
- Stricture development involves excessive extracellular matrix (ECM) deposition due to continuous activation of intestinal myofibroblasts, that further contribute to intestinal fibrogenesis.
- Emerging data suggests that stricture-related intestinal myofibroblasts overexpress a serine protease called fibroblast activation protein (FAP).
- Furthermore, type III collagen deposition is increased during fibrosis in all layers of the intestinal tract, and studies have shown elevated collagen degradation in serum from patients with CD.

2) AIM

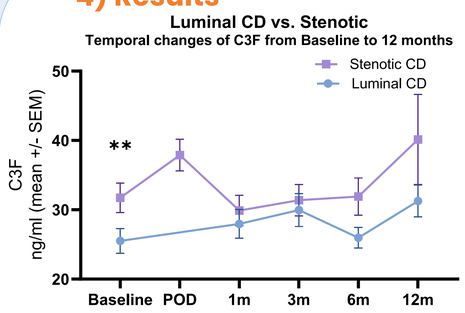
The present study aimed at evaluating the potential of FAP-cleaved type III collagen [C3F] as a serum marker for intestinal fibrosis in CD.

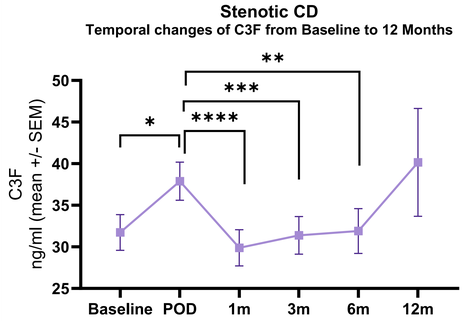
Patient demographics

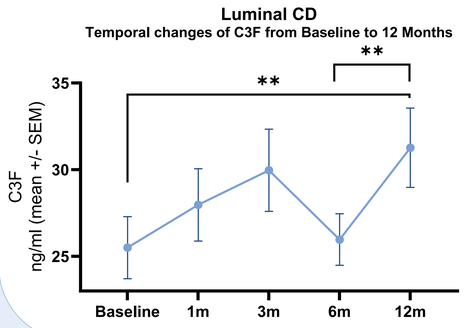
Cohort

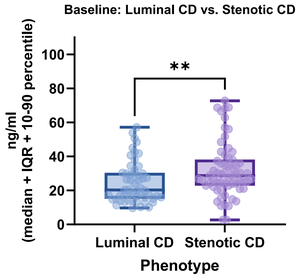
Group	Luminal	Stenotic
Patients, n	49	62
Female, n (%)	18 (37 %)	31 (50 %)
Male, n (%)	31 (63 %)	31 (50 %)
Age, years (Mean [Min, Max])	34.1 [18, 64]	44.1 [18, 86]
BMI, kg/m² (Mean [Min, Max])	24.2 [17.7, 37.9]	25.4 [17.4, 39.0]
CRP, mg/L (Mean [Min, Max])	5.7 [1, 60]	23.9 [1, 218]
Fecal Calprotectin, µg/g (Mean [Min, Max])	1038 [30, 3000]	604.5 [15, 2000]
	HBI , n (%)	
Remission (<5)	23 (48 %)	16 (26 %)
Mild (5-7)	13 (27 %)	13 (21 %)
Moderate (8-16)	12 (25 %)	31 (50 %)
Severe (>16)	0	2 (3 %)

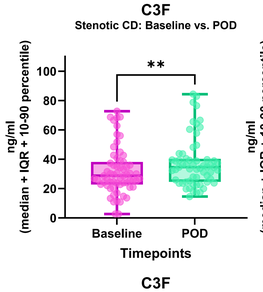
4) Results

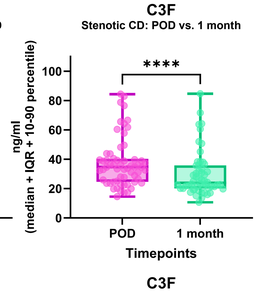


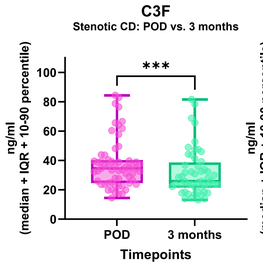


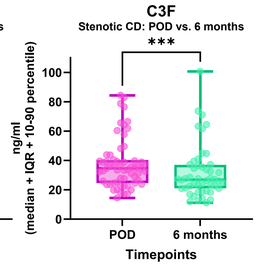


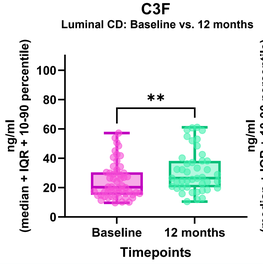












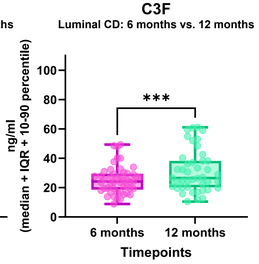


Table 1: ROC curve analysis of C3F for discriminating between CD phenotypes and disease progression timepoints. Significant findings (p<0.05) are highlighted in bold.

C3F	AUC [95% CV]	Sensitivity (%)	Specificity (%)	p-value
Baseline				
Luminal CD vs. Stenotic CD	0.65 [0.54, 0.74]	47.62	70.37	**0.006**
Stenotic Phenotype				
Baseline vs. POD	0.61 [0.51, 0.71]	47.37	70.00	**0.035**
POD vs. 1 month	0.68 [0.57, 0.78]	59.62	70.18	**0.001**
POD vs. 3 months	0.64 [0.53, 0.74]	52.94	73.68	**0.011**
POD vs. 3 months	0.63 [0.52, 0.74]	57.45	70.18	**0.017**
Luminal Phenotype				
Baseline vs. 12 months	0.64 [0.53, 0.75]	44.19	77.78	**0.011**
6 months vs. 12 months	0.60 [0.49, 0.72]	41.86	81.63	0.070

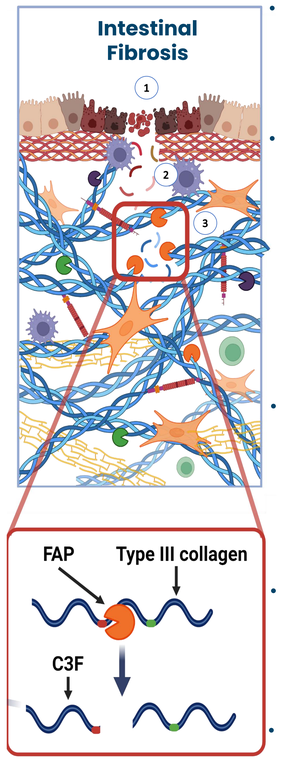
Table 2: Spearman's rank correlation, depicting the relationship between C3F and routine blood demographics, as well as demographics in the Stenotic CD group. Significant findings (p<0.05) are highlighted in bold.

Stenotic CD Markers Demographics	C3F	
Assessed at Baseline	**Rho**	**p-value**
Hemoglobin	-0.146	0.264
Platelets	0.072	0.588
CRP	**0.35**	**0.006**
Fecal calprotectin	0.149	0.336
Length of specimen	0.004	0.974
BMI	-0.088	0.506
Age at inclusion	-0.019	0.885
Disease duration	**-0.257**	**0.048**

Table 3: Spearman's rank correlation between C3F levels measured at Baseline, 1, 3, 6, and 12 months and SES-CD subscore for ileal stenosis assessed at 12 months in patients with luminal CD. Significant findings (p<0.05) are highlighted in bold.

Luminal CD C3F	SES-CD Subscore: Ileal stenosis assessed at 12 months	
Timepoints	**Rho**	**p-value**
Baseline	**0.32**	**0.03**
1 month	0.25	0.133
3 months	**0.30**	**0.049**
6 months	**0.37**	**0.014**
12 months	0.26	0.112

3) METHODS



Generation of C3F fragment in vivo. 1) Fibroblast recruitment and activation at the site of fibrosis. 2) Collagen type III is the main collagenous component of the interstitial matrix. 3) FAP-mediated cleavage of type III collagen by activated fibroblasts results in generation of C3F in the fibrotic tissue and it is released into circulation, that can be measured as biomarker. Figure modified from Rasmus Sund Pedersen.

- The cohort consisted of 49 patients with luminal CD and 62 patients with stenotic CD.
- Clinical assessment was conducted for all patients at baseline and 12 months post study initiation.
- For the luminal phenotype, endoscopy was performed at both time points.
- For the stenotic group, radiographical assessment was done prior to surgery and endoscopy was performed at 12 months.
- C3F was measured in serum for baseline, post-operative day (POD), 1, 3, 6 and 12 months.
- To compare C3F levels at baseline for luminal vs stenotic phenotype, Mann-Whitney U-test was conducted.
- For the stenotic group, mixed-effect analysis (Dunnett's multiple comparison) was conducted to compare C3F levels for baseline vs POD and Spearman's rank correlation was applied.

5) CONCLUSION

C3F is elevated in patients with stenotic CD compared to luminal CD at baseline. For the stenotic group C3F levels are higher after the surgical resection compared to baseline, 1 month, 3 and 6 months, suggesting that C3F reflects **fibroblast activity** during **fibrostenosis** and tissue remodeling following surgery. C3F shows modest discriminatory ability across comparisons, with AUC values ranging from 0.65 to 0.69. The positive correlation with CRP supports the association with inflammation leading to collagen deposition and fibrosis in patients with stenotic CD. C3F shows negative correlation with disease duration suggesting that C3F could reflect fibrosis at early stages of stenotic CD. In patients with luminal CD, C3F levels were significantly higher at 12 months compared to baseline and 6 months, and early C3F levels (baseline, 3 months and 6 months) were significantly positively associated with **ileal stenosis** assessed at 12 months. This suggests that increased C3F may be predictive of future endoscopic disease activity or even a potential relapse. **Thus, the findings highlight the potential use of C3F as a novel biomarker for intestinal fibrosis in CD.**

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