Blood-based biomarkers of type III collagen remodeling as surrogate markers of endoscopic disease activity in patients with Ulcerative Colitis

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1) BACKGROUND

- The chronic inflammation of Ulcerative Colitis (UC) causes excessive extracellular matrix (ECM) remodeling, resulting in clinical complications.
- Currently, endoscopic evaluation remains the gold standard method for determining disease activity. However, novel methods are wanted due to its invasiveness and accompanying patient discomfort.
- Type III collagen is a major component of the intestinal ECM and a target for multiple proteases catalyzing its remodeling in IBD.

3) AIM

We sought to investigate two blood-based neoepitope biomarkers of type III collagen degradation, and fibrosis resolution as surrogate markers of disease activity

4) RESULTS

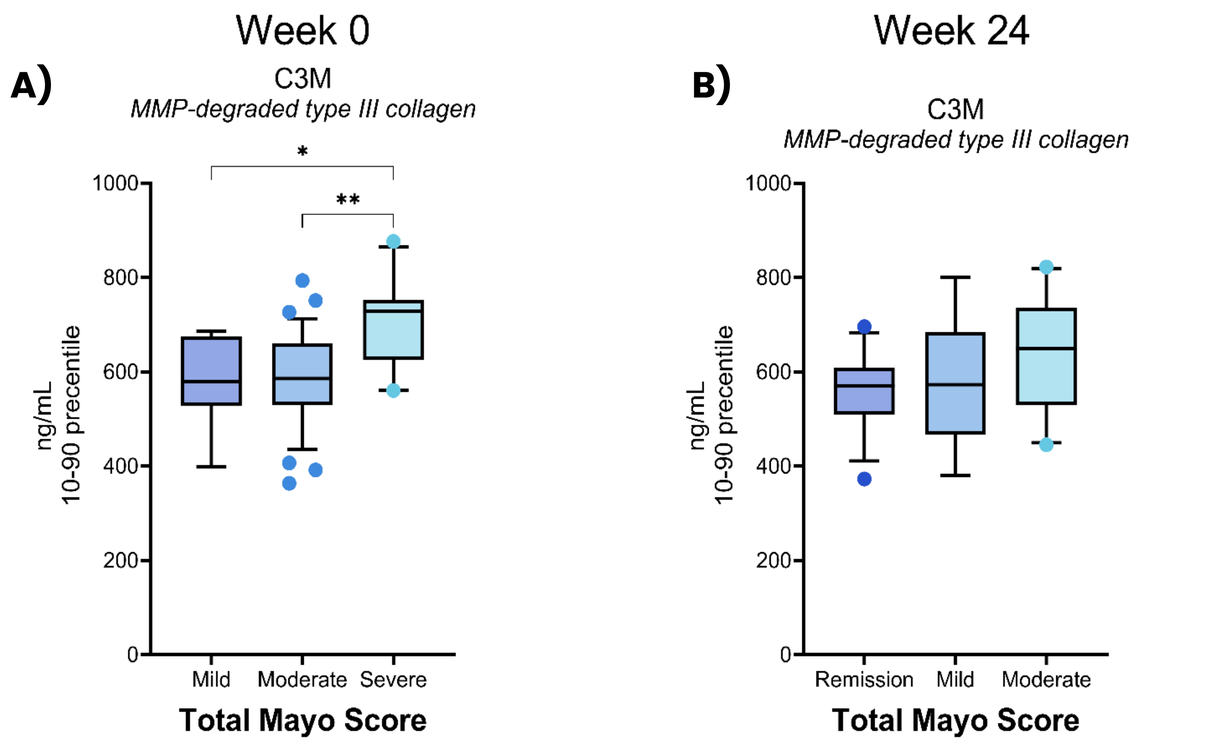


Figure 1. A) Grouping patients according to the TMS at W0, patients with severe endoscopic disease had elevated serum C3M compared to patients with mild or moderate disease ($p<0.05$ and <0.01) **B)** While not statistically significant, a numerical trend of elevated C3M levels with increasing endoscopic disease activity was observed at W24.

The data indicate an association between elevated MMP-9 catalyzed degradation of type III collagen with increasing severity of disease in patients with UC. Thus, the increasing levels of the C3M biomarker reflects the endoscopically assessed mucosal damage.

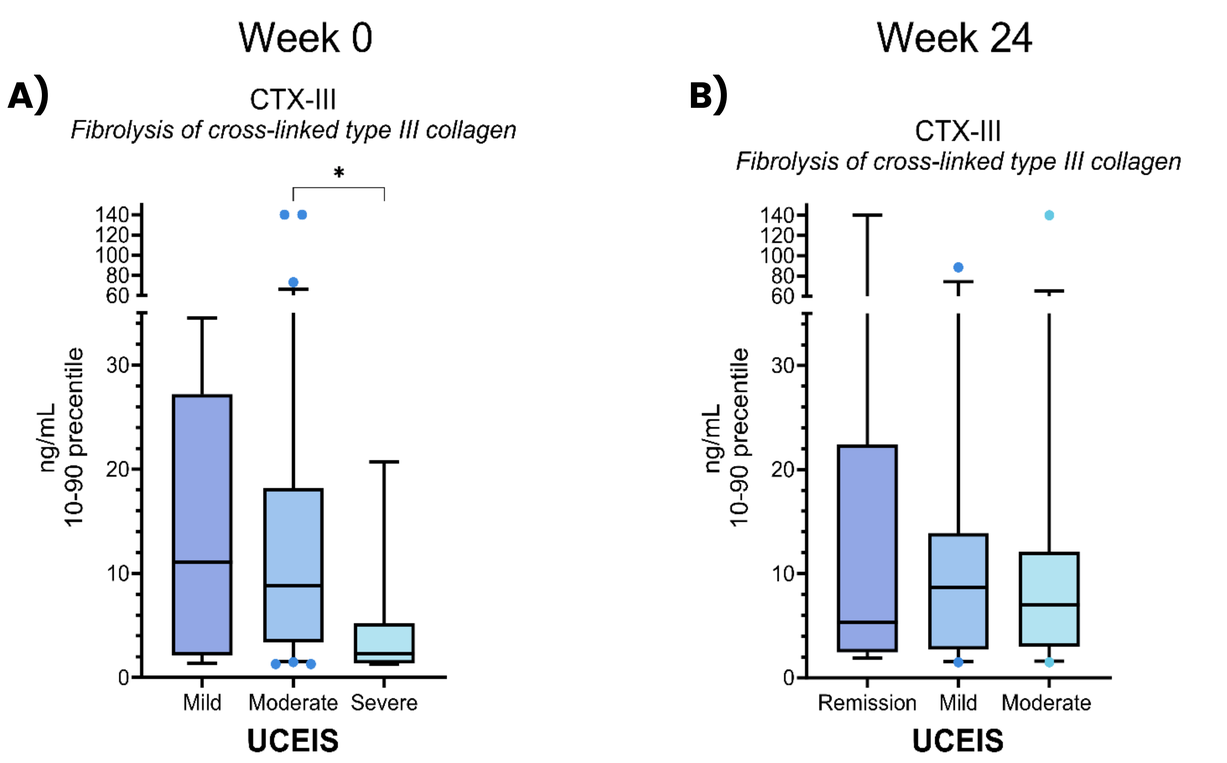
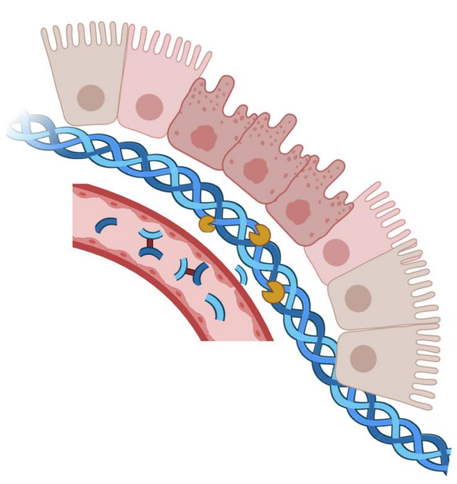


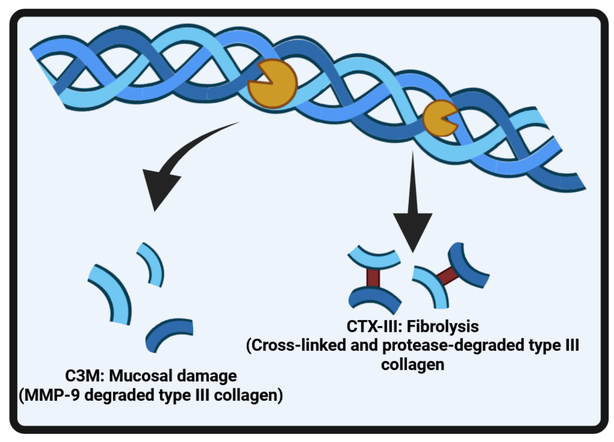
Figure 2. A) Based on the UCEIS, patients with a severe disease presented with reduced CTX-III than moderate disease activity ($p<0.05$) **B)** At W24 no difference in the CTX-III levels between patient groups were observed.

Using the UCEIS score, the CTX-III biomarker reflecting type III collagen resolution was reduced in patients with severe endoscopic disease.

2) METHODS

- Enzyme-linked immunosorbent assays where utilized to quantify MMP-9 degraded (**C3M: Mucosal damage**) and cross-linked and protease-degraded (**CTX-III: Fibrolysis**) type III collagen.
- The biomarkers, C3M and CTX-III were measured in the serum of 51 patients with UC.
- The patients were scored endoscopically at weeks 0 (WO) and 24 (W24) according to the total mayo score (TMS) and the UC endoscopic index of severity (UCEIS)
- Patients were grouped based on endoscopic disease activity and the differences in biomarker levels compared using one-way ANOVA correcting for multiple comparisons using Tukey (parametric) or Dunn's test (nonparametric).





Biomarkers of type III collagen remodeling in the intestine. Proteolytic degradation of type III collagen in the interstitial matrix results in the release of neoepitope-specific protein fragments. MMP-9 catalyzed degradation releases the C3M biomarker reflecting mucosal damage, whereas protease degradation of cross-linked type III collagen releases the CTX-III biomarker, which reflects fibrolysis.

Patient demographics

	Week 0	Week 24
Patients, n	49	47
Age, years (range)	36 (20-73)	ND
Female, n (%) **Male, n (%)**	21 (43% 28 (57%)	ND
BMI, kg/m² (range)	23.6 (17.4-34.9)	ND
Fecal Calprotectin, µg/g (range)	1202 (30-3000)	476 (25-2000)
CRP, mg/L (range)	11 (1-108)	2.2 (1-14)
Total mayo score, n (%)		
Remission	0 (0%)	16 (34%)
Mild	8 (16.3%)	11 (23.4%)
Moderate	31 (63.3%)	13 (27.7%)
Severe	10 (20.4%)	0 (0%)
UCEIS, n (%)		
Remission	0 (0%)	8 (17%)
Mild	5 (10.2%)	14 (29.8%)
Moderate	34 (69.4%)	19 (40.4%)
Severe	9 (18.4%)	0 (0%)
Extent, n (%) **Normal/E1/E2/E3**	0 (0%)/13 (26.5%)/13 (26.5%)/23 (47%)	7 (14.9%)/16 (34%)/6 (12.8%)/12 (25.5%)

5) CONCLUSION

- **C3M was elevated at Week 0 in UC patients with severe endoscopic disease activity according to the Total Mayo Score**
- **The fibrolysis biomarker, CTX-III, was significantly elevated in patients with moderate endoscopic disease at week 0 and numerically elevated in mild disease compared to severe disease activity**

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