# The crosslinked type III collagen biomarker, CTX-III, reflects fibrosis resolution and is related to intervention and survival in chronic liver disease


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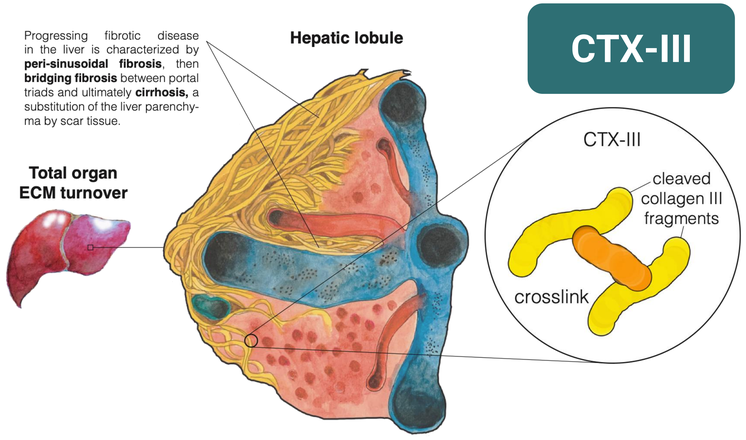
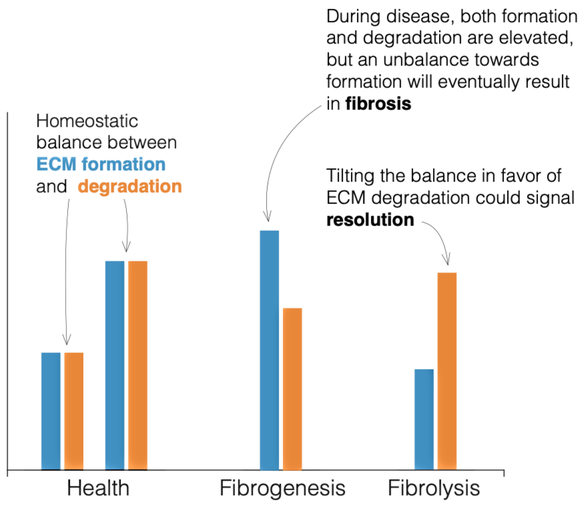
## Background

- Liver fibrosis progresses by deposing increasing amounts of crosslinked collagens in the extracellular matrix (ECM), destroying the liver parenchyma in the process. Treatments that hamper fibrosis could trigger the degradation of crosslinked fragments. A biomarker that measures the destruction of crosllinked collagen could open a window into the evolution of disease and the effectivity of therapy.

We hypothesize that circulating fragments of crosslinked collagen type III (**CTX-III**) can be detected and measured to reflect fibrinolysis, and thus biomark fibrosis resolution.

Progressing fibrotic disease in the liver is characterized by **peri-sinusoidal fibrosis**, then **bridging fibrosis** between portal triads and ultimately **cirrhosis,** a substitution of the liver parenchyma by scar tissue.

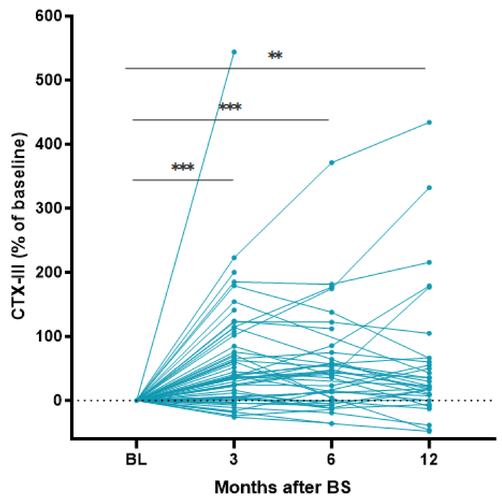



## Results

### CTX-III detects fibrinolysis after surgery

**CTX-III increases after bariatric surgery**



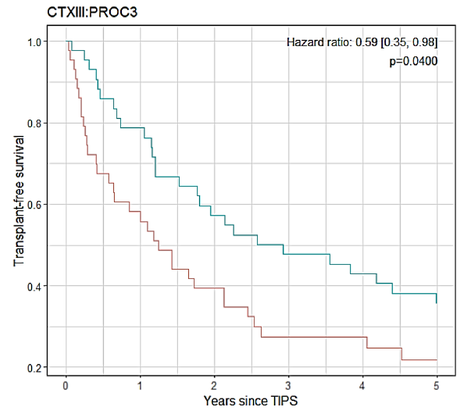

**CTX-III** increases after bariatric surgery. Interestingly, **CTX-III** levels remain high 1 year after surgery, suggesting the presence of a sustained response to treatment.

**CTX-III** increase points to a wave of crosslinked collagen type III degradation (fibrinolysis).
As overweight patients develop liver and adipose fibrosis, **CTX-III** suggests clinical improvement.

**Bariatric surgery patients**

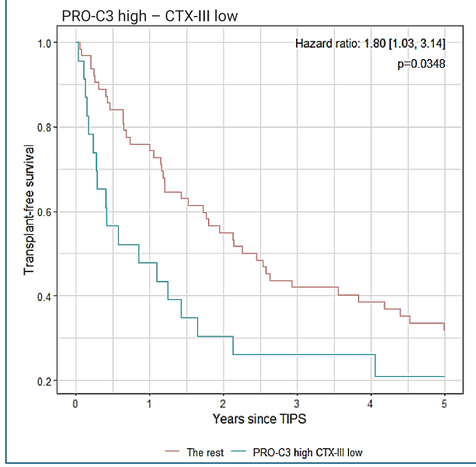
| | Baseline (n=65) | Baseline for biopsy (n=33) | Follow-up (n=33) | *P*-value (n=33) |
|---|---|---|---|---|
| **BMI, kg/m²** | 41.9 (37.5-46.1) | 41.9 (37.5-44.8) | 31.4 (27.8-34.5) | **<0.001** |
| **Age, years** | 44 (39-52) | 44 (39-52) | 44 (39-52) | NA |
| **Sex, female** | 40 (62%) | 18 (55%) | 18 (55%) | NA |
| **Type 2 diabetes** | 16 (24.6%) | 8 (24%) | 4 (12%) | 0.339 |
| **AST, U/L** | 23.5 (20.0-29.0) | 23.0 (18.5-30.0) | 24.5 (21.8-27.3) | 0.922 |
| **ALT, U/L** | 29.0 (23.0-39.0) | 31.0 (25.0-37.0) | 22.0 (17.0-31.0) | **0.006** |
| **GGT, U/L** | 26.0 (18.0-39.0) | 31.0 (18.5-39.0) | 19 (12.0-21.0) | **<0.001** |
| **CRP mg/L** | 4.4 (2.1-7.6) | 4.2 (2.1-6.9) | 0.9 (0.5-1.9) | **<0.001** |
| **Fasting glucose** | 6.1 (5.6-6.6) | 6.3 (5.7-6.6) | 5.4 (5.2-5.6) | **<0.001** |
| **HbA1c mmol/mol** | 37.0 (34.0-38.0) | 36.5 (33.8-38.0) | 33.5 (32.0-36.3) | **0.001** |
| **Fibrosis 0/1/2/3/4,** | 2/55/8/0/0 | 1/28/4/0/0 | 4/28/1/0/0 | 0.195 |
| **Steatosis 0/1/2/3, n** | 34/21/9/0 | 18/11/4/0 | 30/3/0/0 | **0.003** |
| **Ballooning 0/1/2, n** | 2/39/24 | 0/22/11 | 27/5/1 | **<0.001** |
| **Inflammation** | 6/44/15/0 | 3/23/7/0 | 15/18/0/0 | **<0.001** |
| **NAS** | 0/6/19/16/10/13/1/ | 0/2/11/10/5/5/0/0/0 | | **<0.001** |
| **PRO-C3, ng/ml** | 8.8 (8.0-10.2) | 8.8 (8.0-10.0) | 9.2 (7.8-10.4) | 0.161 |
| **CTX-III, ng/ml** | 12.2 (4.2-19.4) | 12.9 (4.2-18.6) | 14.2 (5.5-31.8) | **0.001** |

### CTX-III (fibrolysis) and PRO-C3 (fibrogenesis) reveal different survival after TIPS




**PRO-C3** is a marker of fibrogenesis (progressing fibrosis). By combining it with **CTX-III**, we identified a group of patients with decompensated cirrhosis treated with Transjugular Intrahepatic Porto-systemic Shunt (TIPS) to improve portal hypertension who had a high **CTX-III** to **PRO-C3** and a significantly longer survival after treatment.

Conversely, patients with high **PRO-C3** and low **CTX-III** have a shorter survival.
These results suggest that an ECM equilibrium tending to fibrinolysis is correlated to significantly longer life, even in patients with decompensated cirrhosis.




**TIPS patients**

| | |
|---|---|
| **Sex** | |
| Female | 33 (38%) |
| Male | 53 (62%) |
| **Age** | |
| Median (Q1, Q3) | 59.0 (52.2, 65.0) |
| **CHILD-PUGH Score** | |
| A | 15 (17%) |
| B | 54 (63%) |
| C | 17 (20%) |
| **Deaths or liver transplants within 5yrs** | |
| n(%) | 60 (70%) |
| **Deaths with 5yrs** | |
| n(%) | 55 (64%) |
| **Liver transplants with 5yrs** | |
| n(%) | 5 (6%) |
| **Follow up time (yrs)** | |
| Median (Q1, Q3) | 1.8 (0.6, 5.0) |
| **PROC3 Baseline (ng/mL)** | |
| Median (Q1, Q3) | 29.9 (18.8, 46.3) |
| **CTX-III Baseline (ng/mL)** | |
| Median (Q1, Q3) | 2.5 (2.0, 4.0) |
| **CTX-III:PROC3** | |
| Median (Q1, Q3) | 9.3 (5.0, 20.8) |

## Conclusions

- **CTX-III** is a biomarker engineered to detect enzymatically degraded **crosslinked collagen type III**.
- **CTX-III** levels increase after bariatric surgery, suggesting it is possible to measure systemic response to surgical intervention.
- **CTX-III:PRO-C3** ratio detects a subpopulation of cirrhotic patients who respond to TIPS with significantly longer survival.

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