Weight dependent, weight independent and non-pharmacological effects on fibroblast activity in metabolic dysfunction associated steatotic liver disease (MASLD)

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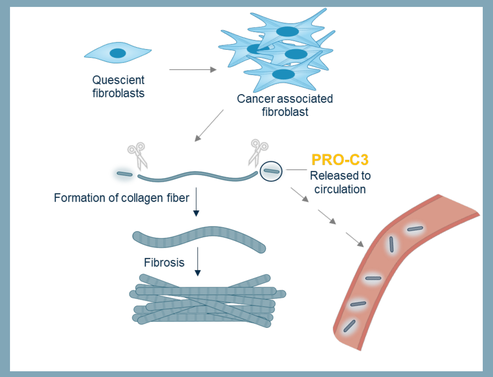
BACKGROUND

It is well established that fibroblasts are activated by metabolic dysfunction and are a central component of liver function decline and death. Fibroblast activities, both type III and type VI collagen formation, have been shown to be highly prognostic for outcome of liver, heart and kidney related events in MAFLD populations. Fibroblast activity in man, may both be inhibited by weight dependent and independent mechanisms, and as such monitoring fibroblast activities is essential.



METHODS

To shed light on the effect of weight loss on other organs, we performed a post-hoc analysis of data from elderly subjects and investigated the relationship between weight loss and bone loss using the biomarker of bone resorption CTX-I. Additionally, we used recently published data on the liver fibrosis biomarker PRO-C3 and the pro-fibrotic, fibroblast hormone PRO-C6/endotrophin, from both weight loss studies, and pharmacological interventions by Resmiterom and GLP-1 receptor agonists.

RESULTS – weight loss leads to increased bone resorption, with no change in bone formation

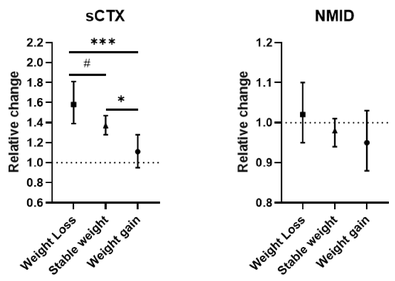


Figure 1. *Bone resorption (sCTX) and bone formation (NMID) were measured at baseline and after 2 years in 806 subjects with a baseline BMI of 29kg/m². The subjects were divided according to whether they showed a weight loss exceeding 5%, were stable, or showed a weight gain of more than 5% over two years.*

RESULTS - Bariatric surgery leads to bone loss

Bariatric surgery leads to excessive bone resorption

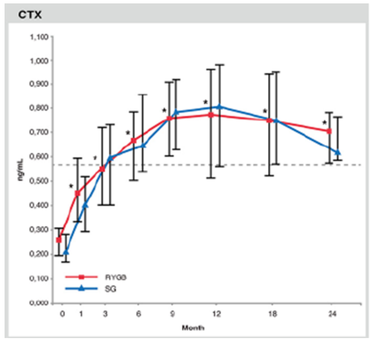


Figure 2*. CTX-I levels following Roux-en-Y bypass surgery or sleeve gastrectomy (Muschitz et al, JCEM, 2015)*

RESULTS - Very Low Calorie Diet (VLCD) reduces the fibrotic drive in the liver

PRO-C6 showed no changes following 12 weeks of Very Low Calorie Diet

PRO-C3 showed a rapid decline upon initiation of Very Low Calorie Diet

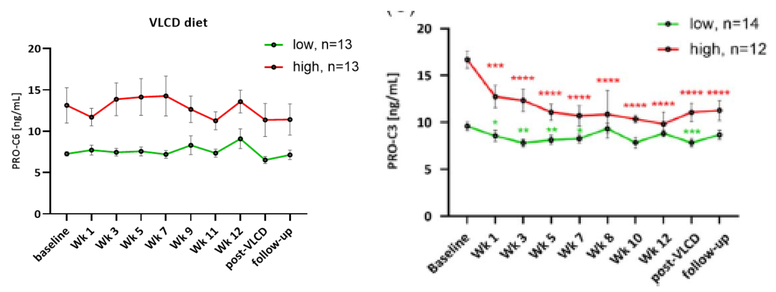


Figure 3*. Study subjects were divided into high or low biomarker status at baseline (by the median), and the levels of PRO-C6 (A) and PRO-C3 were monitored at all timepoints during the trial.*

RESULTS – Drug dependent effects on PRO-C3 and PRO-C6

Dulaglutide induces a significant lowering of PRO-C6 levels in obese subjects with co-morbid diabetes

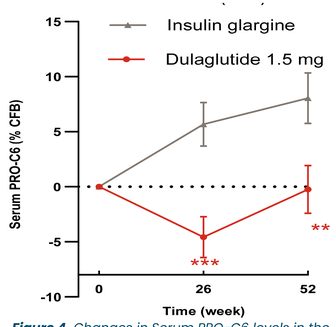


Figure 4. *Changes in Serum PRO-C6 levels in the AWARD-7 trial (n=330).*

Resmetirom induces a weight-independent lowering of PRO-C3 levels in MASH patients

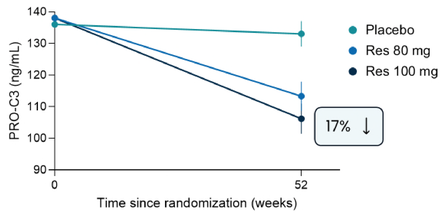


Figure 5. *Changes in Serum PRO-C3 levels in the MAESTRO-NASH trial (n=966) (Anstee et al, EASL, 2024)*

Semaglutide induces a significant lowering of PRO-C3 levels in MASH patients

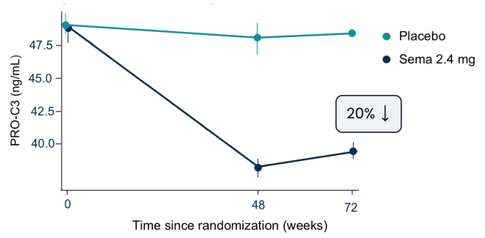


Figure 6*. Changes in Serum PRO-C3 levels in the ESSENCE trial (n=1200) (Newsome et al, EASL, 2024)*

'PRO-C6 levels indicate increased mortality across indications

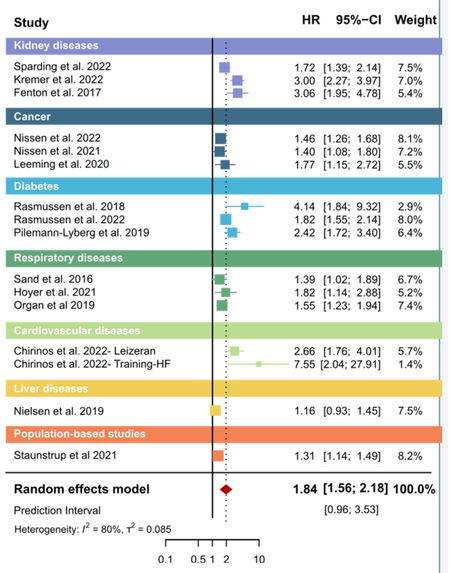
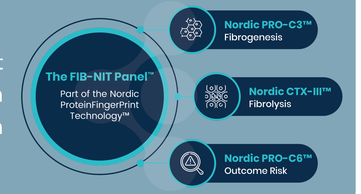


Figure 6. *Overall mortality; Adjusted effect sizes with 95 % confidence intervals per standard deviation increase in baseline PRO –C6 levels. All estimates were adjusted for age and sex. Weights (representing the relative contribution of each study to the overall assessment) are calculated from the random-effects model. Abbreviations: HR: Hazard Ratio, 95 % CI: 95 % confidence interval. (Genovese et al, Matrix Biology, 2025).*

Key Messages

Pharmacological and non-pharmacological induction of weight loss results in different deactivation of fibroblasts activities, which may have divergent efficacy on heart and liver related outcomes. Furthermore, weight dependent and independent mechanisms of deactivation fibroblasts may result in additional effects on bone and muscle. This understanding may be needed when designing the optimal intervention strategy, including possible combination regimens, for the individual MAFLD patient.



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