Metabolic, biochemical and histological effects of semaglutide in a CDAA-HFD-induced non-obese and biopsy-confirmed rat model of NASH with progressive fibrosis and tumor development

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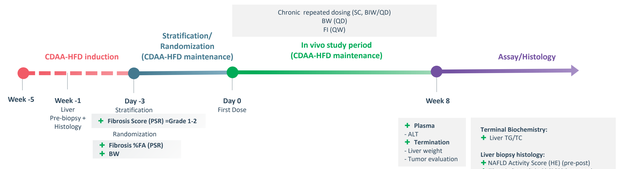
Background & Aim

The glucagon-like-peptide (GLP)-1 analogue semaglutide, currently approved for the treatment of type 2 diabetes and obesity, is in late-stage clinical development for non-alcoholic steatohepatitis (NASH). The present study evaluated the therapeutic effects of semaglutide in a Choline-Deficient l-Amino-Acid-defined High-Fat Diet-induced (CDAA-HFD) non-obese rat model of NASH with progressive fibrosis and tumor development.

Study outline



#	Group name	*n* in group	Animal model	Dose	Route of administration	Dosing Frequency
1	Chow	8	LEAN-CHOW	NA	SC	BIW
2	Vehicle	15	CDAA-HFD	NA	SC	BIW
3	Semaglutide	15	CDAA-HFD	30 nmol/kg	SC	QD
4	Chow reversal (Vehicle)	15	CDAA-HFD	NA	SC	BIW

Metabolic and biochemical parameters

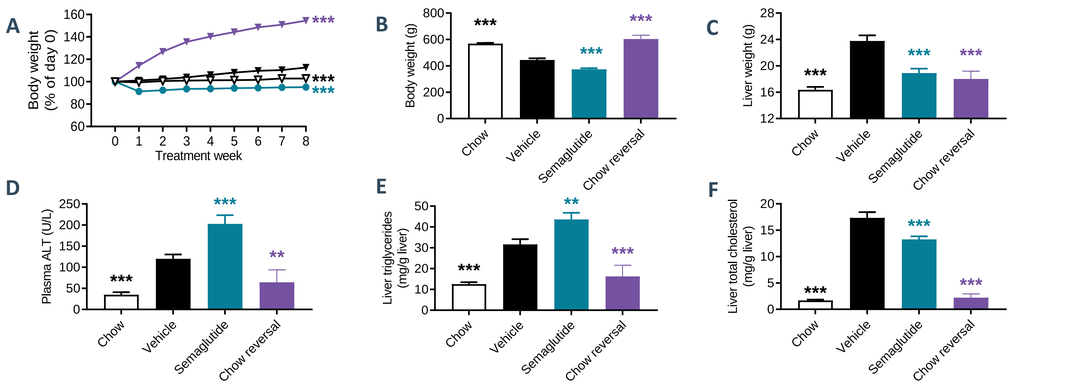


Figure 1. Semaglutide reduces body weight, liver weight and biochemical parameters in CDAA-HFD non-obese rat model of NASH. (A) Body weight change relative to baseline (day 0). **(B)** Terminal body weight (g). **(C)** Terminal liver weight. **(D)** Terminal plasma alanine aminotransferase (ALT). **(E)** Terminal liver triglycerides. **(F)** Terminal liver total cholesterol. *p<0.05, **p<0.01, ***p<0.001 compared to corresponding Vehicle control (Dunnett's test one-factor linear model).

Histopathological NAFLD Activity Score and Fibrosis Score

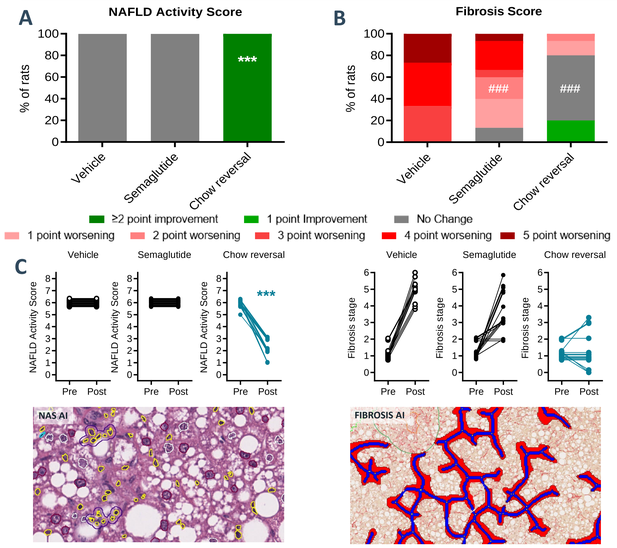


Figure 2. Semaglutide improves liver histopathological fibrosis score in CDAA-HFD non-obese rat model of NASH. **(A)** NAFLD Activity Score (NAS) determined by Gubra Histopathological Objective Scoring Technique (GHOST) deep learning-based image analysis. **(B)** Fibrosis Score (Ishak), manually scored. **(C)** Comparison of individual pre-post NAS and individual pre-post Fibrosis stage. ***p<0.001 compared to vehicle group (One-sided Fisher's exact test with Bonferroni correction). ###p<0.001 for ≥3 point worsening compared to vehicle group (One-sided Fisher's exact test). Bottom panels: Representative HE and PSR photomicrographs used for GHOST evaluation.

Histological quantitative markers of steatosis, inflammation and fibrosis

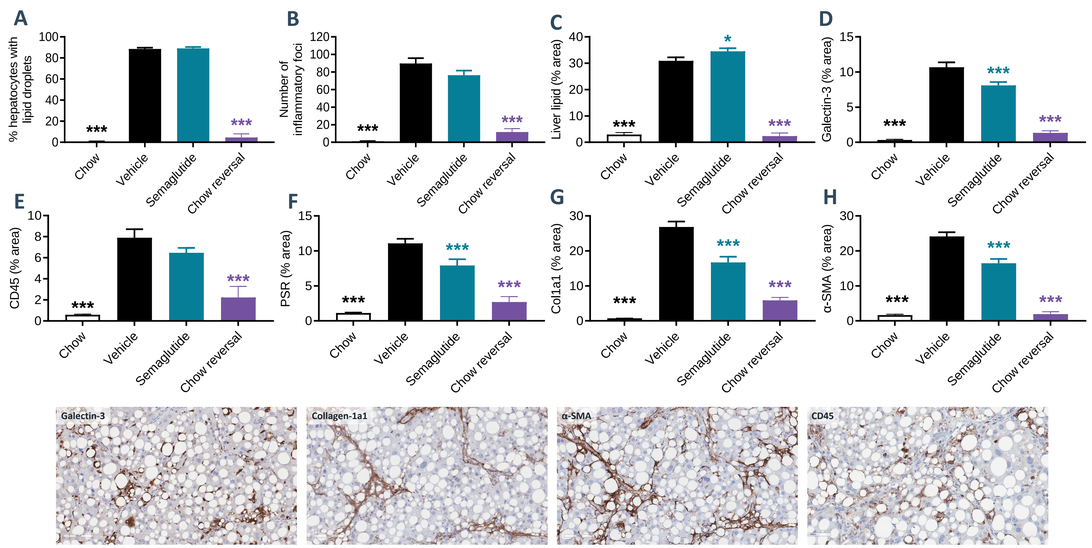


Figure 3. Semaglutide improves quantitative liver histological markers for fibrosis in CDAA-HFD non-obese rat model of NASH.
Histomorphometric assessments were performed by GHOST deep learning-based image analysis on scoring-associated variables (panels A-B) and conventional IHC image analysis (panels C-H). **(A)** % hepatocytes with lipid droplets. **(B)** Number of inflammatory foci. **(C)** % area with liver lipids. **(D)** % area of galectin-3. **(E)** % area of CD45 **(F)** % area of PSR. **(G)** % area of collagen-1a1. **(H)** % area of alpha-smooth muscle actin (α-SMA) as marker for stellate cell activation. Mean ± SEM. *p<0.05, ***p<0.001 compared to vehicle group (Dunnett's test one-factor linear model). Bottom panels: Representative galectin-3, collagen 1a1, α-SMA and CD45 photomicrographs for semaglutide treatment group (scale bar, 100 µm).

Surface tumor evaluation

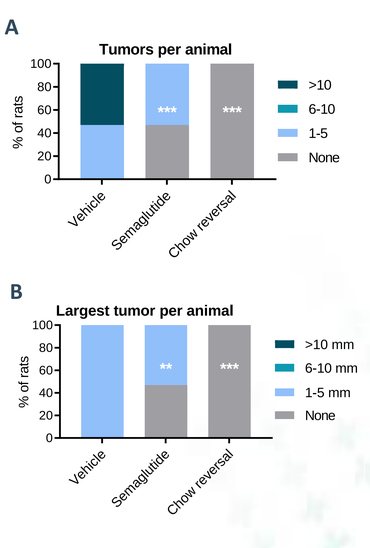


Figure 4. Semaglutide improves tumor burden in CDAA-HFD non-obese rat model of NASH.
Macroscopic tumor assessment for **(A)** Number of tumors per animal, and **(B)** Largest tumor per animal (diameter, mm). **p<0.01, ***p<0.001 compared to vehicle group (Dunnett's test one-factor linear model).

CONCLUSION

- Semaglutide reduces body weight, hepatomegaly and liver total cholesterol and preserve levels of plasma ALT and liver triglycerides.
- Semaglutide do not improve NAFLD Activity Score, albeit significantly prevents ≥3-point worsening in fibrosis score.
- Semaglutide reduces quantitative histological markers of fibrosis and stellate cell activation.
- Semaglutide improves surface evaluated tumor burden.
- Pre-biopsy confirmed CDAA-HFD non-obese rat model of NASH allows exploration of drug efficacy for progressive fibrosis and tumor development.