

Metabolic, biochemical, histological, and transcriptomic effects of semaglutide in the GAN diet-induced and biopsy-confirmed ob/ob mouse model of NASH



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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 advanced clinical development for non-alcoholic steatohepatitis (NASH). In line with clinical findings, semaglutide has been demonstrated to improve parameters of NASH including NAFLD Activity Score in the GAN DIO-NASH mouse model.

The present study aimed to evaluate the metabolic, biochemical, histological and transcriptomic effects of 10 weeks treatment with semaglutide in the GAN ob/ob-NASH mouse model with progressive fibrosis.

1 Study outline

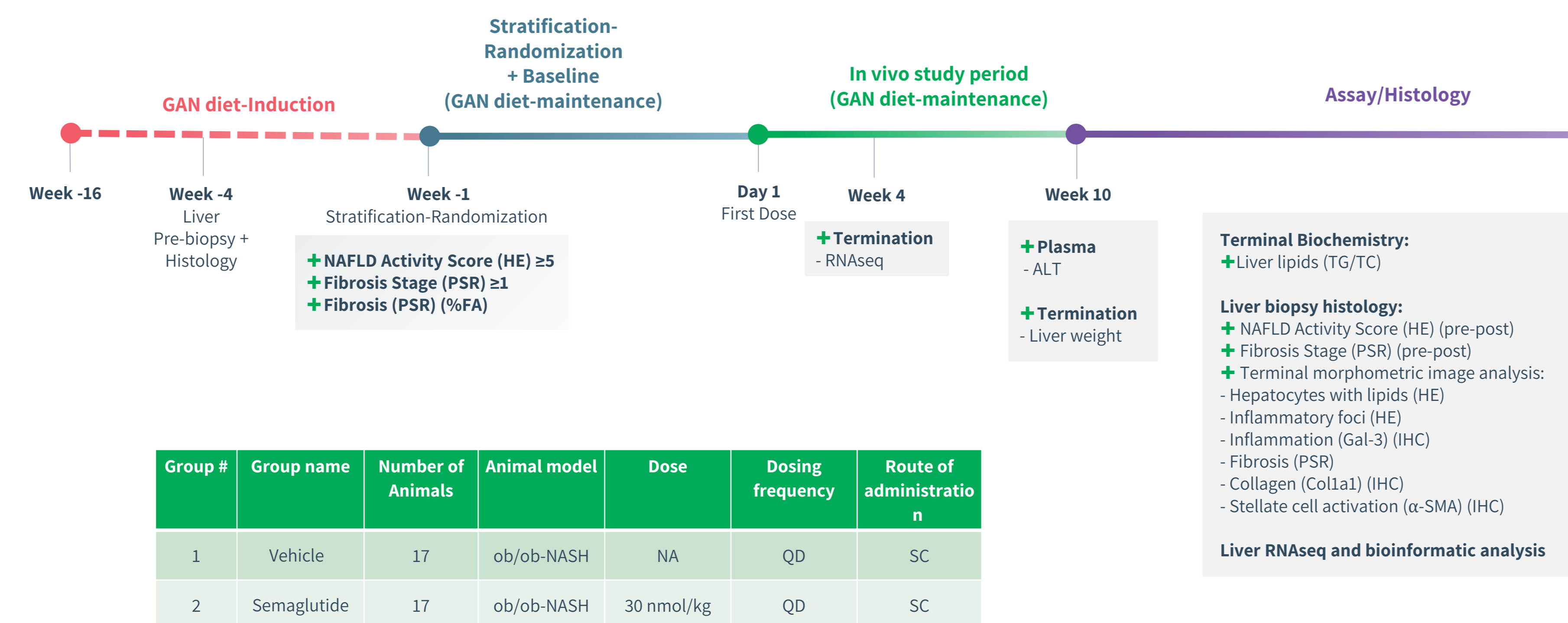


Figure 1. Study outline, groups and treatments. ALT: alanine aminotransferase; TC: total cholesterol; TG: triglycerides; QD: once daily; SC: subcutaneous; PO: per oral.

2 Metabolic and biochemical parameters

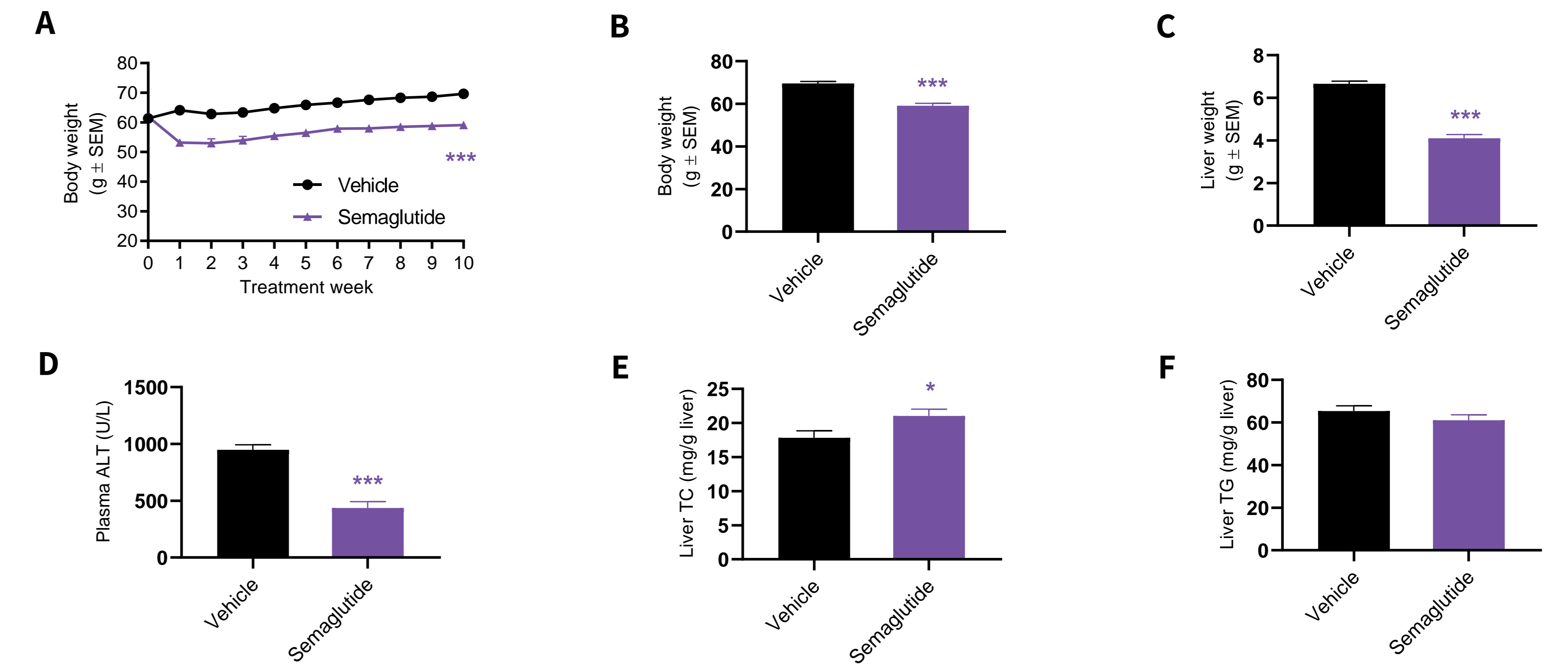


Figure 2. Semaglutide improves metabolic and biochemical parameters in GAN ob/ob-NASH mice. (A) Absolute body weight during study period. (B) Terminal body weight. (C) Terminal liver weight. (D) Terminal plasma alanine aminotransferase (ALT). (E) Terminal liver total cholesterol. (F) Terminal liver triglycerides. * $p < 0.05$, *** $p < 0.001$ compared to corresponding vehicle control (Dunnett's test one-factor linear model).

3 NAFLD Activity Score and Fibrosis stage

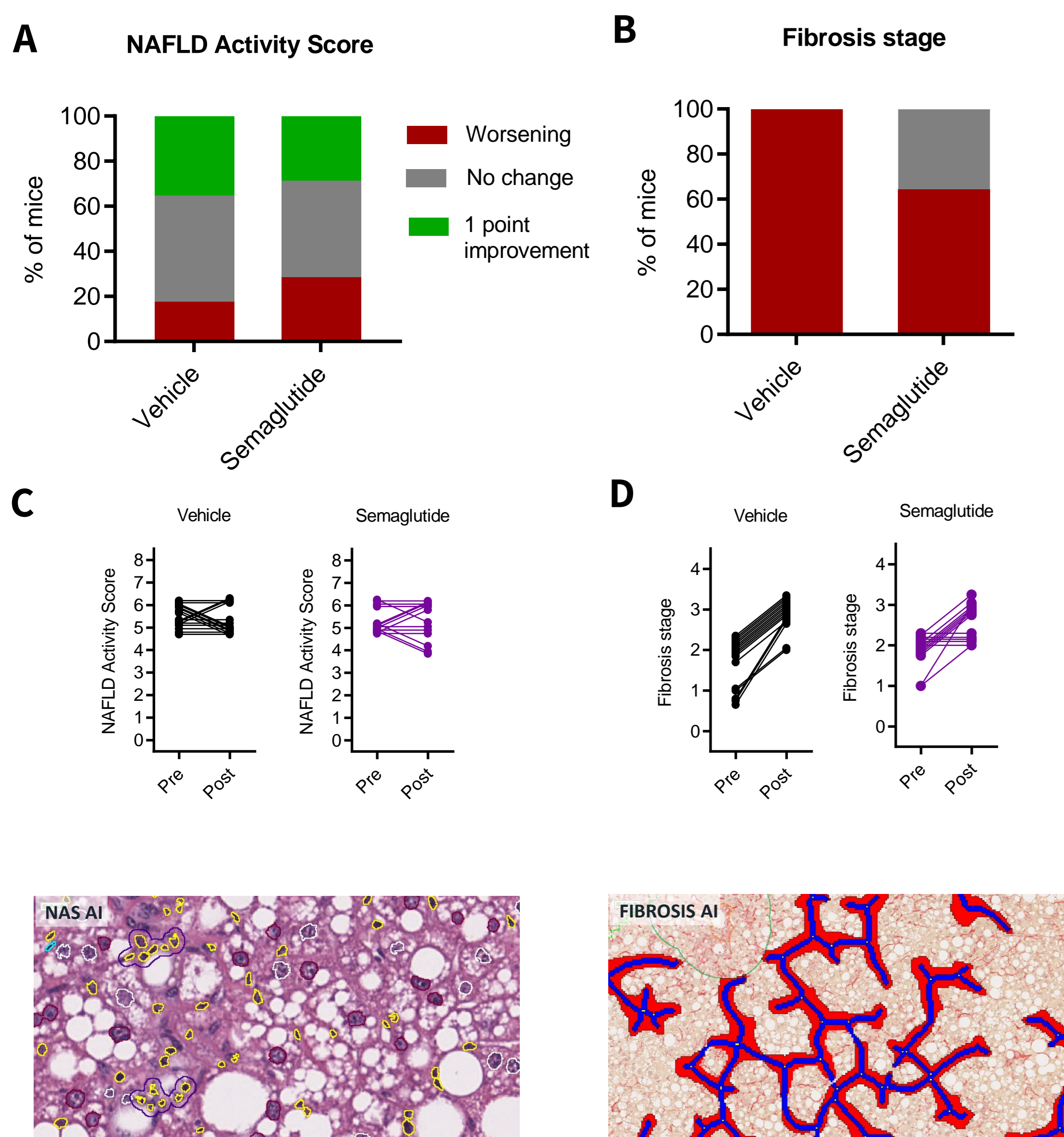


Figure 3. Semaglutide has no effect on histopathological scores in GAN ob/ob-NASH mice. Histopathological scores were determined by Gubra Histopathological Objective Scoring Technique (GHOST) deep learning-based image analysis. (A) NAFLD Activity Score (NAS). (B) Fibrosis stage. (C, D) Comparison of individual pre-post NAS and individual pre-post Fibrosis stage. Bottom panels: Representative HE and PSR photomicrographs used for GHOST evaluation.

4 Histological quantitative markers of steatosis, inflammation and fibrosis

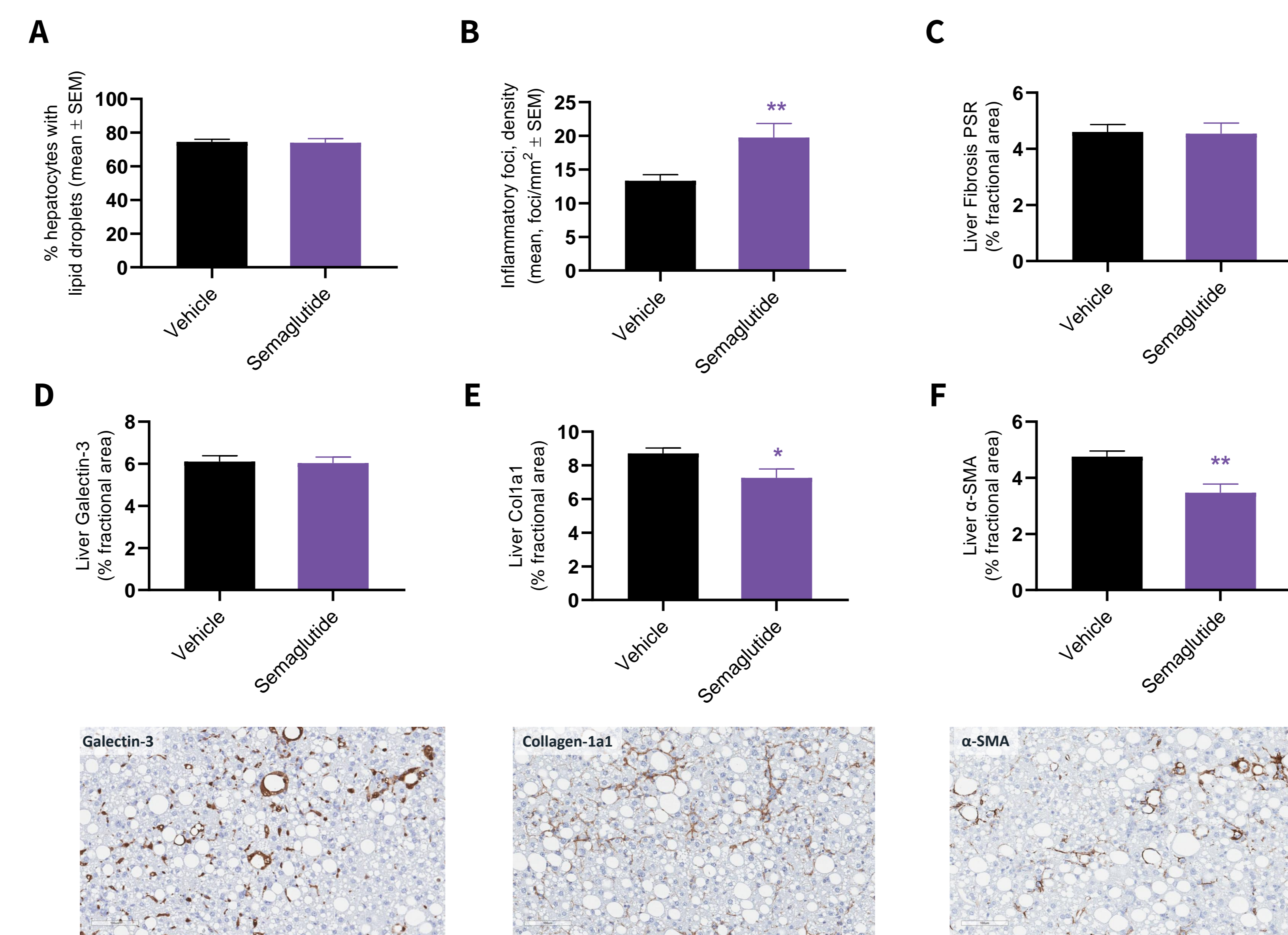


Figure 4. Semaglutide decreases histological markers for fibrogenesis in GAN ob/ob-NASH mice. Histomorphometric assessments were performed by GHOST deep learning-based image analysis on scoring-associated variables (panels A-B) and conventional IHC image analysis (panels C-F). (A) % hepatocytes with lipid droplets. (B) Number of inflammatory foci. (C) % area of PSR. (D) % area of galectin-3. (E) % area of collagen-1a1. (F) % area of alpha-smooth muscle actin (α -SMA) as marker for stellate cell activation. Mean \pm SEM. * $p < 0.05$, ** $p < 0.01$ to corresponding vehicle group (Dunnett's test one-factor linear model). Bottom panels: Representative galectin-3, collagen 1a1 and α -SMA photomicrographs for semaglutide treatment group (scale bar, 100 μ m).

5 Transcriptomic profile for fibrosis and inflammation

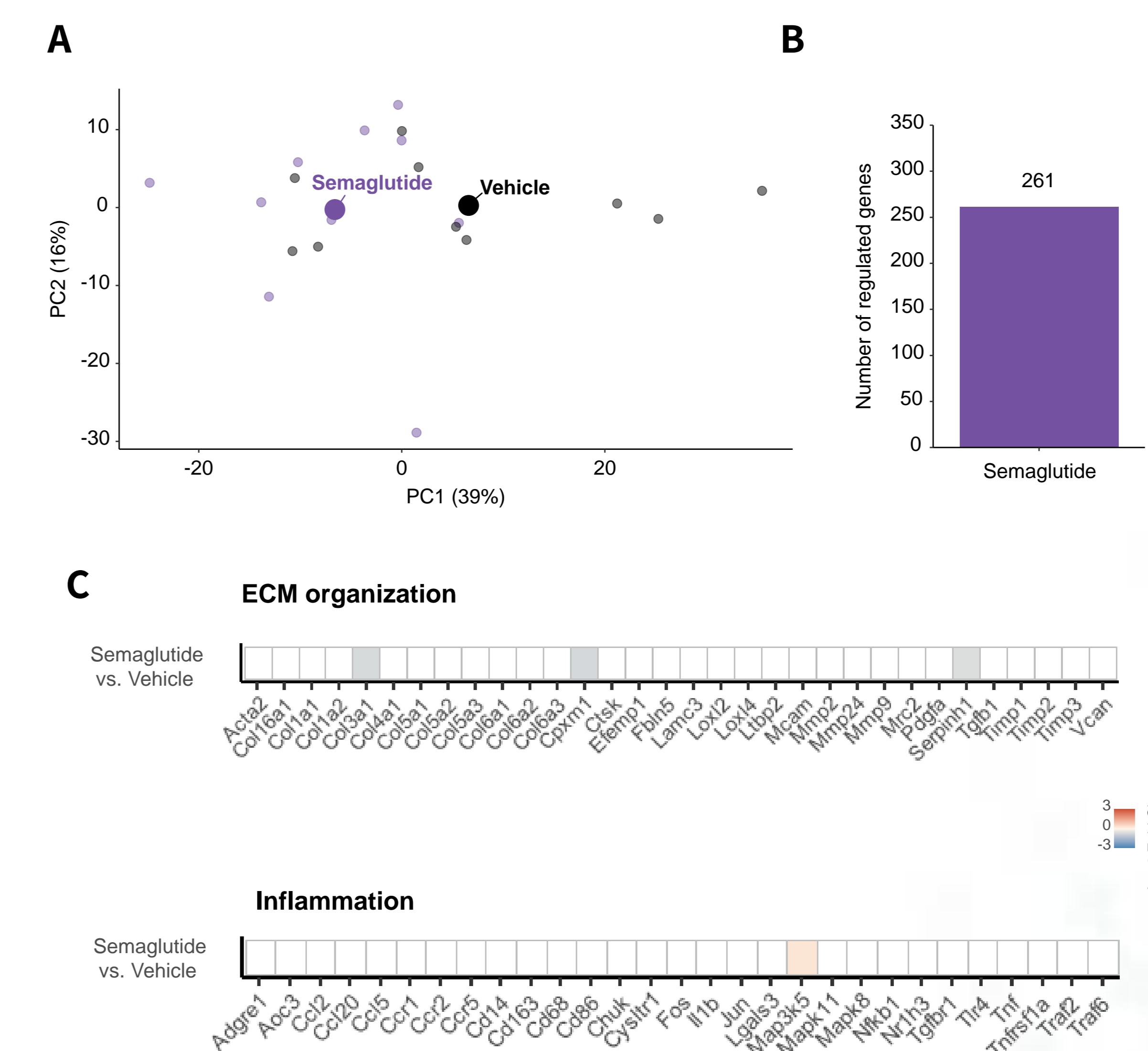


Figure 5. Semaglutide does not affect fibrosis- or inflammation-associated genes in GAN ob/ob-NASH mice. (A) Principal component analysis (PCA) of samples based on top 500 most variable gene expression levels. (B) Differentially expressed genes. (C) Regulation of hepatic extracellular matrix (ECM) and inflammation candidate genes (log₂-fold change compared to corresponding DIO-NASH vehicle control mice). Blue and red colour gradients indicate significantly ($p < 0.05$) down-regulated and up-regulated gene expression, respectively. White boxes indicate genes not significantly regulated ($p > 0.05$).

CONCLUSION

- + Semaglutide reduces body weight, hepatomegaly and plasma ALT while increases liver TC content.
- + Semaglutide does not affect NAFLD Activity Score and fibrosis stage.
- + Semaglutide reduces quantitative histological markers of stellate cell activation and collagen I, without affecting steatosis or inflammation markers.
- + Semaglutide minimally influences transcriptomic profile and has no major impact on fibrosis- or inflammation-associated genes.
- + These findings demonstrate lack of clinical translatability for semaglutide in the GAN ob/ob-NASH mouse model.