

Hepatoprotective effects of semaglutide and tirzepatide in the GAN diet-induced obese and biopsy-confirmed mouse model of MASH

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Background & Aim

Semaglutide (GLP-1 receptor agonist) and tirzepatide (dual GLP-1 receptor and glucose-dependent insulinotropic polypeptide (GIP) receptor agonist) are in late-stage clinical development for MASH. The present study aimed to compare metabolic, biochemical, histological, and transcriptomic outcomes of semaglutide and tirzepatide monotherapy in the translational GAN diet-induced obese (DIO) and biopsy-confirmed mouse model of MASH with liver fibrosis.

1 Study outline

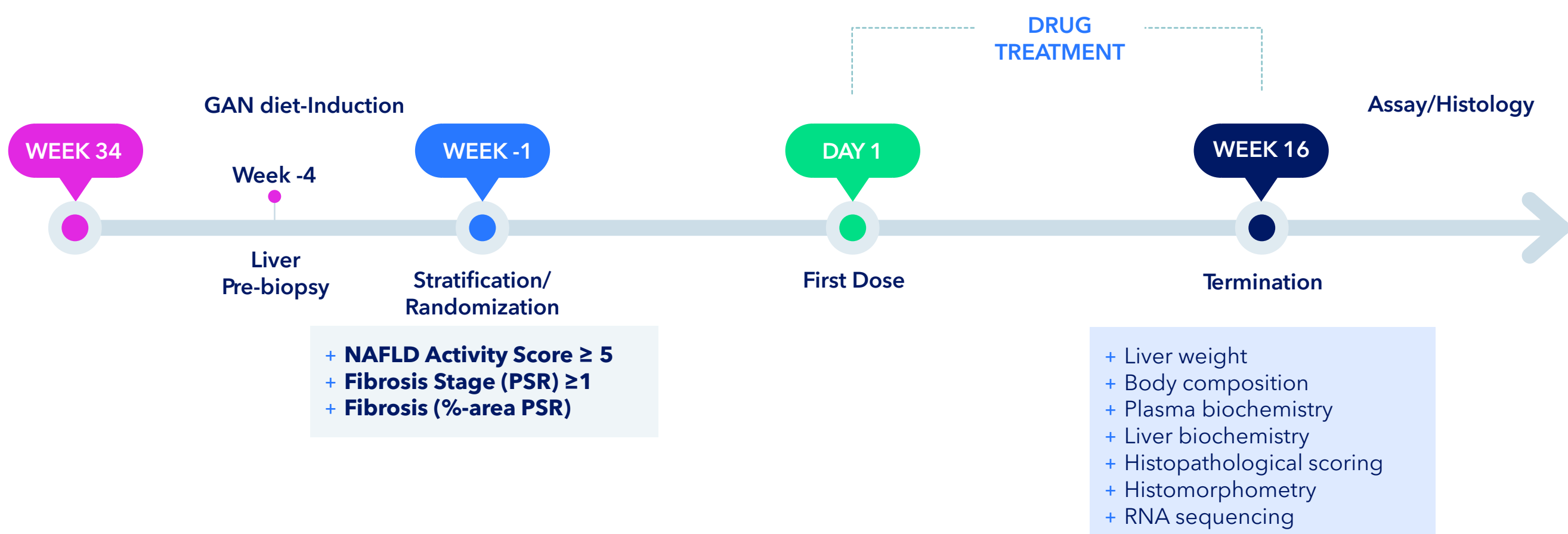


Figure 1. Study outline. Abbreviations: SC; subcutaneous, QD; once daily, NA; not applicable, GAN; Gubra Amylin NAS.

2 Body weight and composition

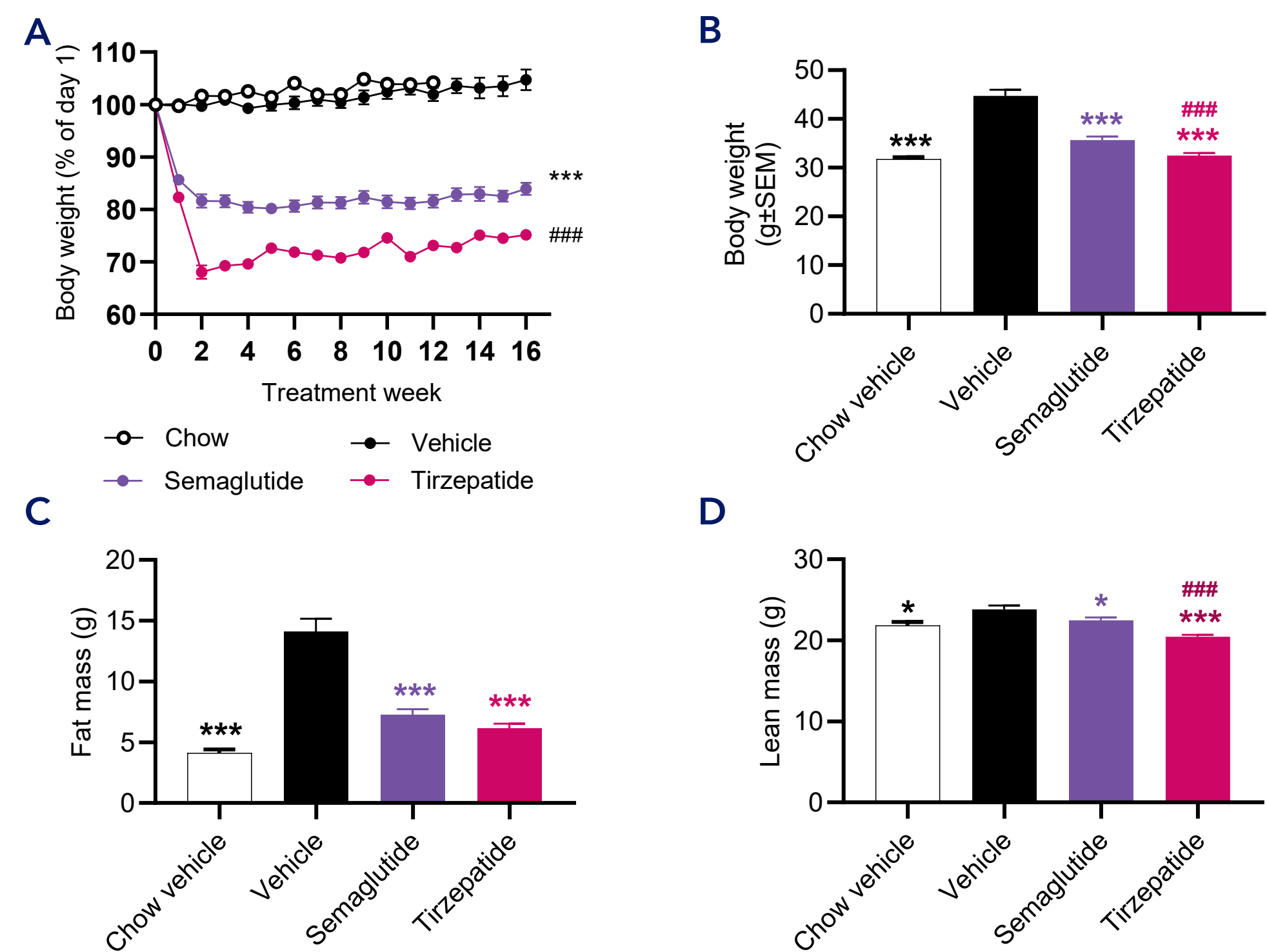


Figure 2. Sustained body weight loss induced by semaglutide and tirzepatide. (A) Relative body weight during study period. (B) Body weight (g). (C) Whole-body fat mass (termination) by echoMRI. (D) Whole-body lean mass (termination) by echoMRI. * $p < 0.05$, *** $p < 0.001$ compared to Vehicle, ** $p < 0.01$, *** $p < 0.001$ compared to semaglutide. (Dunnett's test one-factor linear model).

3 Metabolic and biochemical parameters

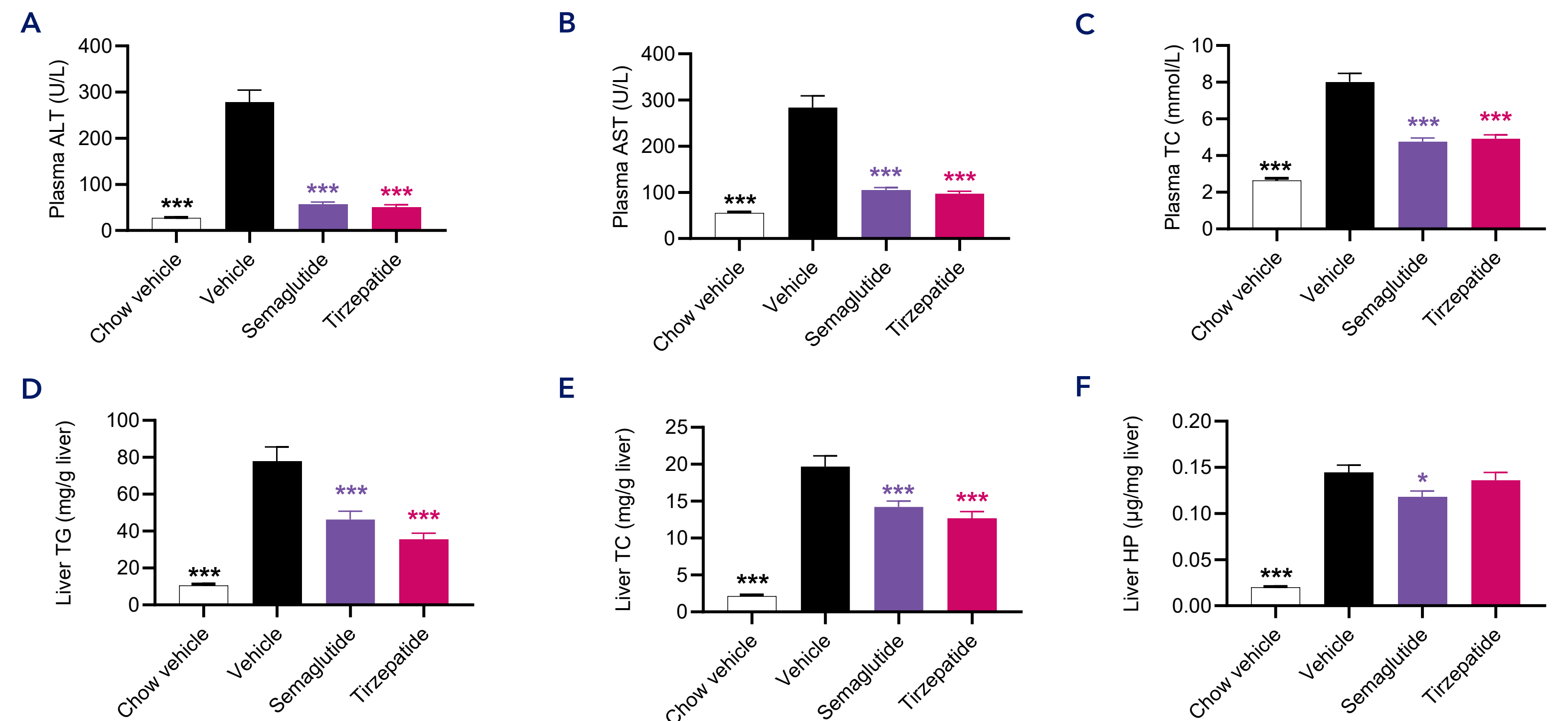


Figure 3. Semaglutide and Tirzepatide treatment reduced liver weight and biochemical parameters (A) Terminal liver weight. (B) Terminal plasma alanine aminotransferase (ALT). (C) Terminal plasma aspartate transaminase (AST). (D) Terminal plasma total cholesterol (TC). (E) Liver triglycerides (TG). (F) Liver hydroxyproline (HP). * $p < 0.05$, *** $p < 0.001$, compared to Vehicle, compared to Semaglutide. (Dunnett's test one-factor linear model).

4 NAFLD Activity Score and Fibrosis Stage

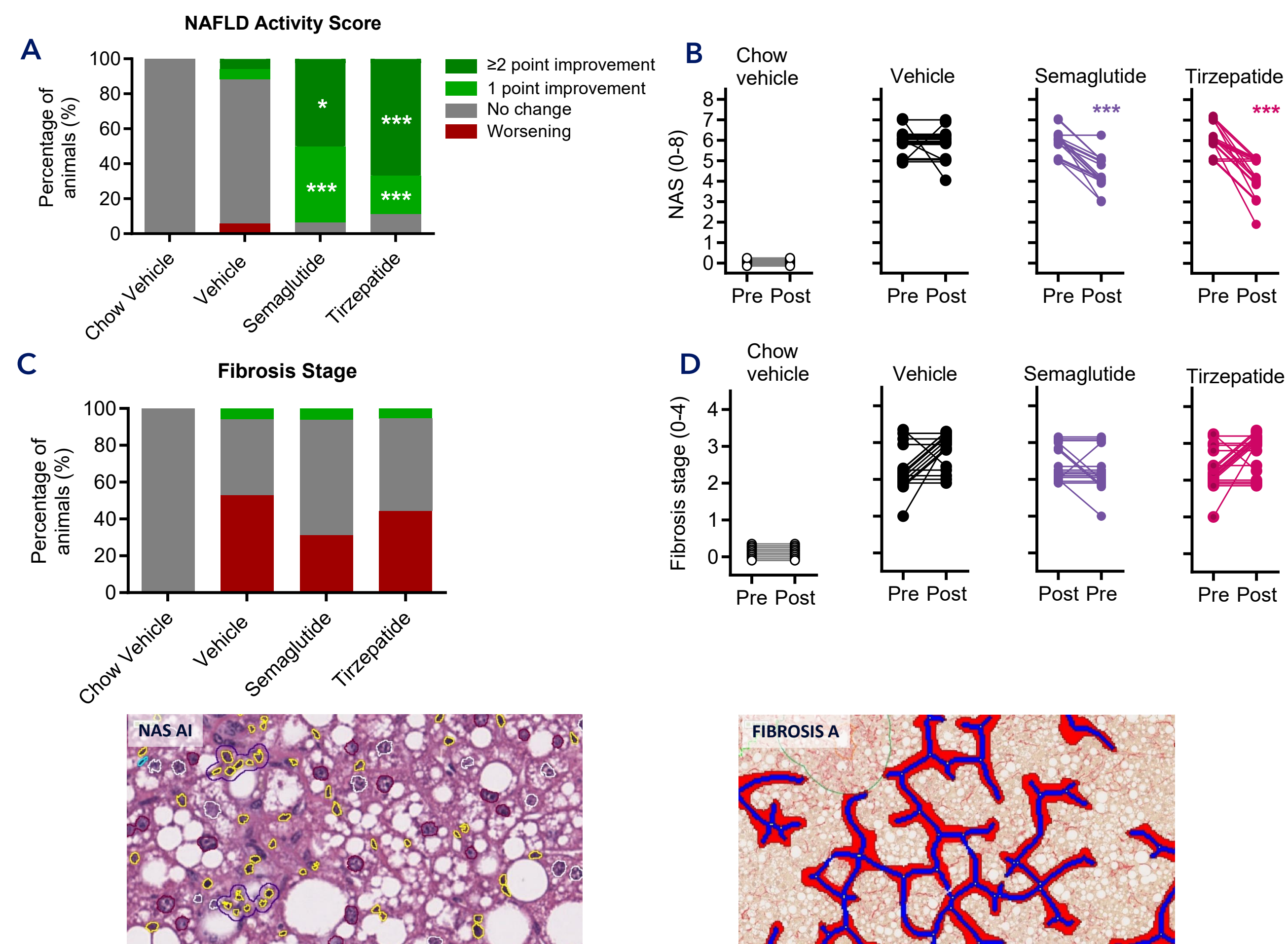


Figure 4. Semaglutide and tirzepatide improve NAFLD Activity Score but not fibrosis stage. Histopathological scores were determined by Gubra Histopathological Objective Scoring Technique (GHOST) deep learning-based image analysis. (A) NAFLD Activity Score (NAS). (B) Individual pre-post NAS. (C) Fibrosis stage. (D) Individual pre-post fibrosis stage. * $p < 0.05$, *** $p < 0.001$ compared to vehicle (One-sided Fisher's exact test).

5 Histological markers of steatosis, inflammation, fibrosis & fibrogenesis

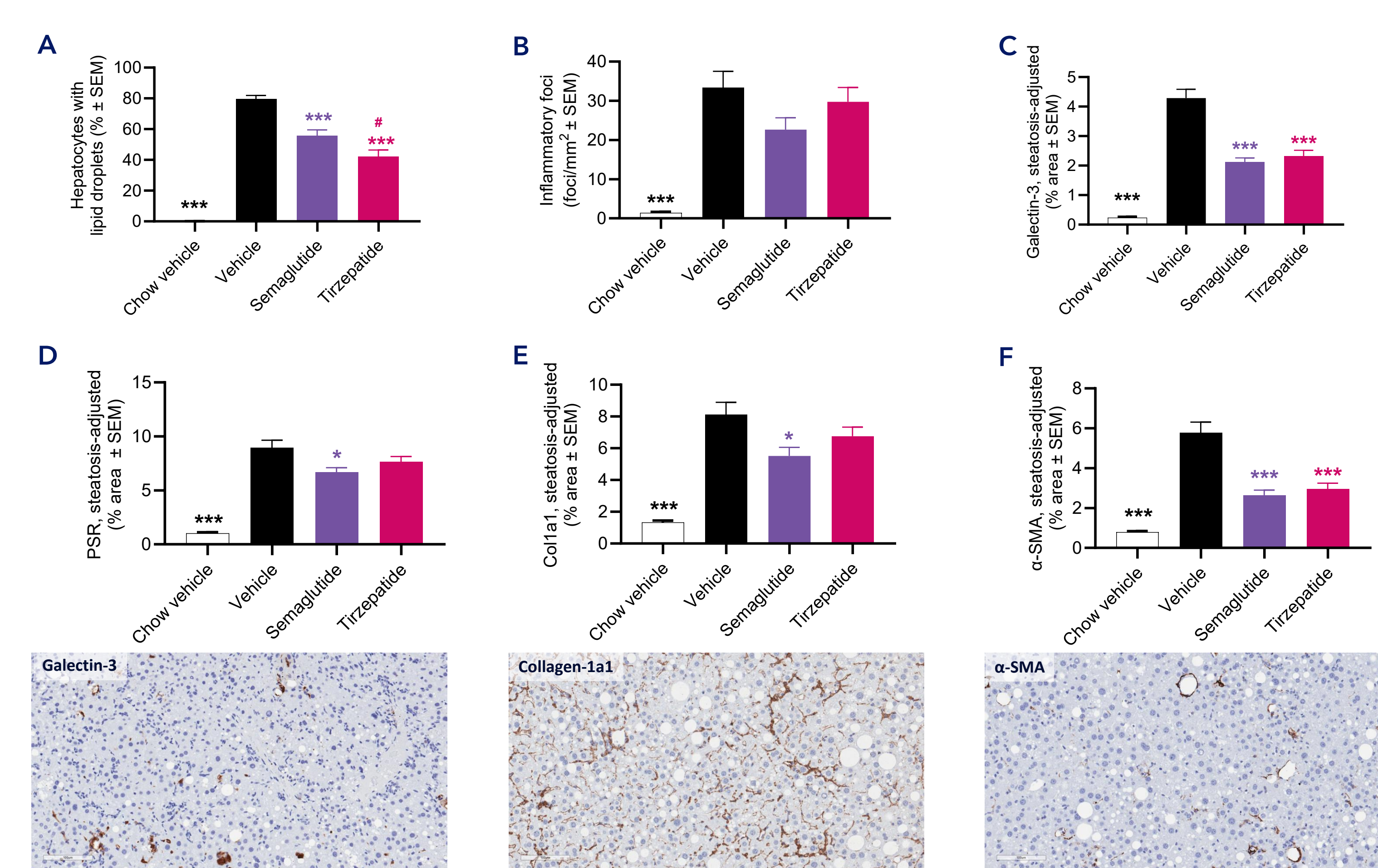


Figure 5. Semaglutide and tirzepatide improve quantitative histological markers of steatosis and inflammation. Histomorphometric assessments were performed by GHOST deep learning-based image analysis on scoring-associated variables (panels A-B) and conventional IHC image analysis (panels C-F). (A) % hepatocytes with lipid droplets. (B) Number of inflammatory foci. (C) % area of galectin-3. (D) % area of PSR. (E) % area of collagen-1a1 (Col1a1). (F) % area of alpha-smooth muscle actin (α -SMA, marker of stellate cell activation). Mean $\pm$ SEM. Chow vehicle vs Vehicle are compared with t-test. Treatment groups are compared to Vehicle with one factor linear model followed by Dunnett's test. * $p < 0.05$, *** $p < 0.001$ compared to vehicle, * $p < 0.05$ compared to semaglutide. Bottom panels: Representative photomicrographs of galectin-3, α -SMA and Col1a1 staining (scale bar, 100 μ m).

6 Hepatic transcriptomic profile

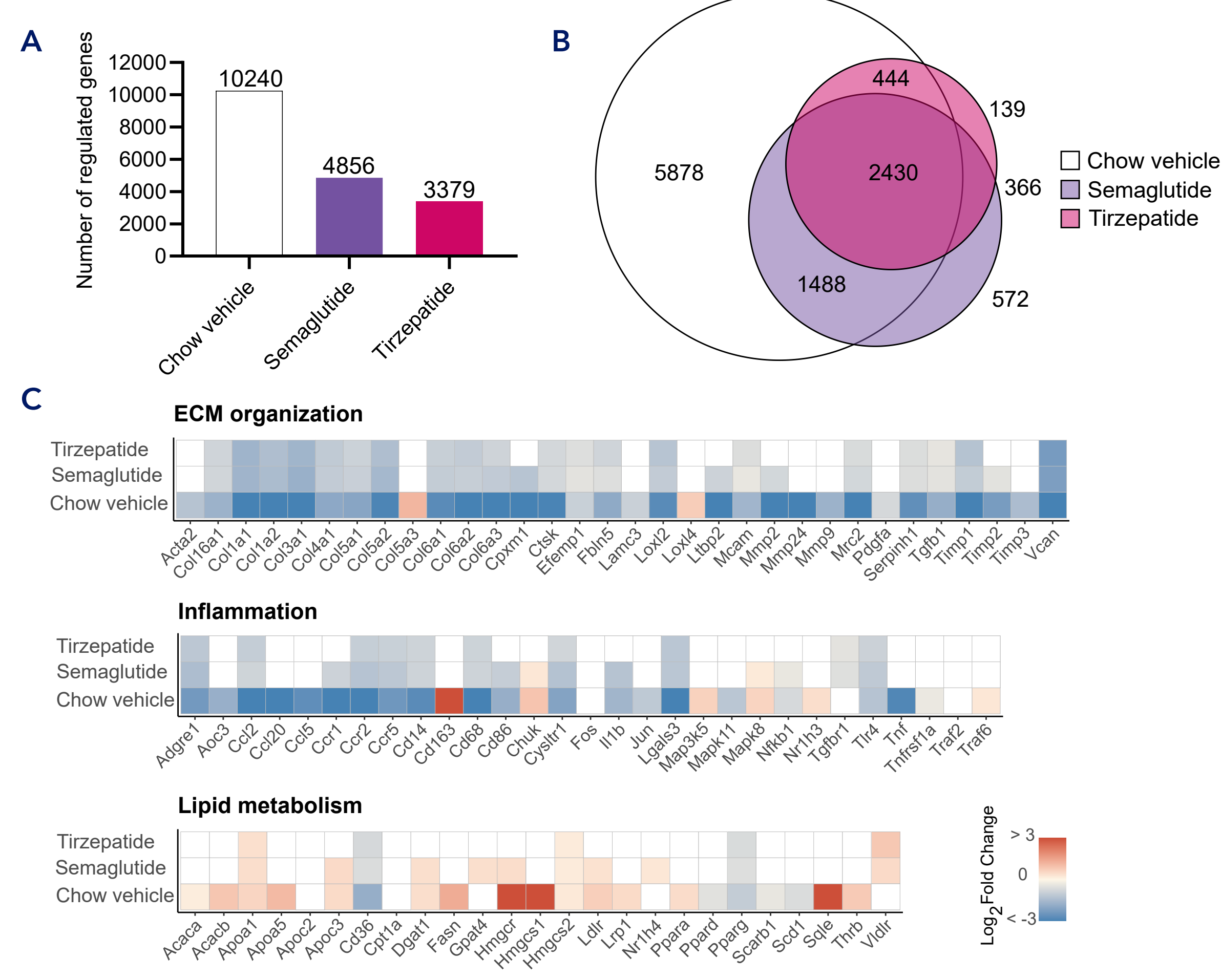


Figure 6. Semaglutide and tirzepatide impact number of differentially expressed genes. (A) Differentially expressed genes. (B) Gene regulation overlap. (C) Changes in candidate gene expression markers of extracellular matrix (ECM), inflammation and lipid metabolism (log2-fold change compared to corresponding DIO-MASH 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 and tirzepatide induce robust weight loss (17% and 25% respectively) via reduction in both whole-body fat and lean tissue mass.
- + Semaglutide and tirzepatide improve transaminases, plasma/liver total cholesterol and triglyceride levels
- + Semaglutide and tirzepatide promote significant 2-point improvement in NAS
- + Benefits on NAS are supported by reduced quantitative histological markers of steatosis and inflammation.
- + Semaglutide and tirzepatide shows no significant effect on fibrosis stage, albeit semaglutide reduces biochemical (HP) and quantitative histological markers of fibrosis (PSR, Col1a1).
- + Semaglutide and tirzepatide reduce histological marker of fibrogenesis (α -SMA).
- + Semaglutide and tirzepatide robustly impact hepatic transcriptome signatures and suppress gene markers of ECM remodelling.

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