

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

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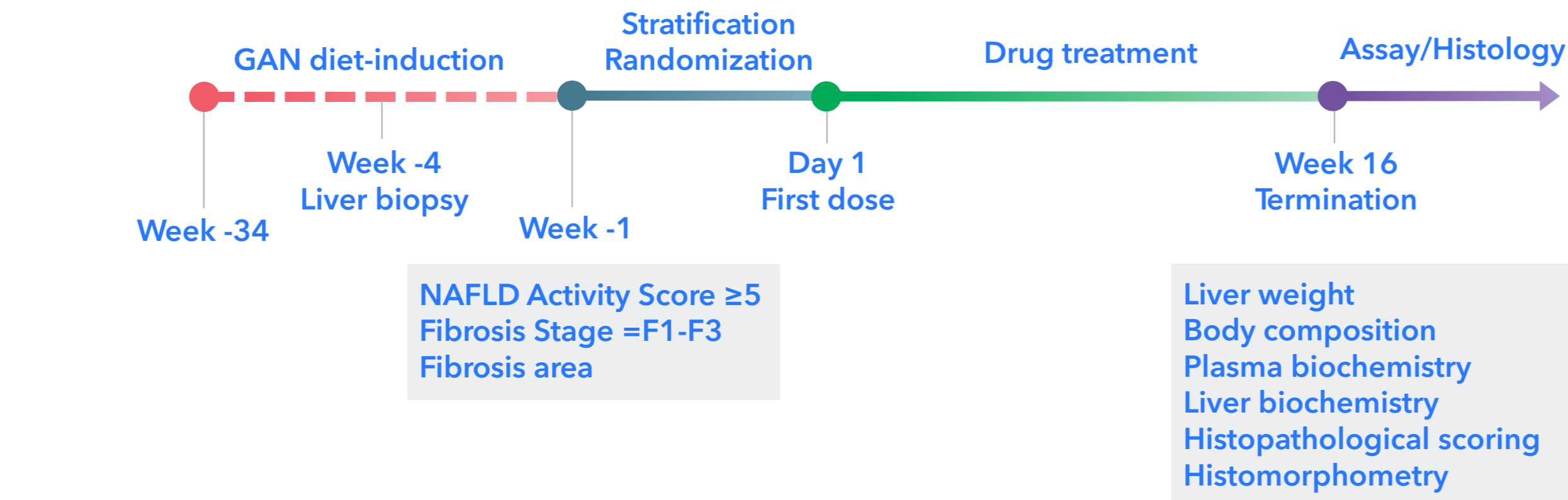
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Background & Aim

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 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



| Group | Animal | Gender | Number of animals | Treatment | Administration route | Dosing frequency | Dosing concentration |
|-------|-----------|--------|-------------------|-------------|----------------------|------------------|----------------------|
| 1 | LEAN-CHOW | Male | 10 | Vehicle | SC | QD | NA |
| 2 | DIO-MASH | Male | 18 | Vehicle | SC | QD | NA |
| 3 | DIO-MASH | Male | 18 | Semaglutide | SC | QD | 10 nmol/kg |
| 4 | DIO-MASH | Male | 18 | Tirzepatide | SC | QD | 10 nmol/kg |

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

2 Metabolic and biochemical parameters

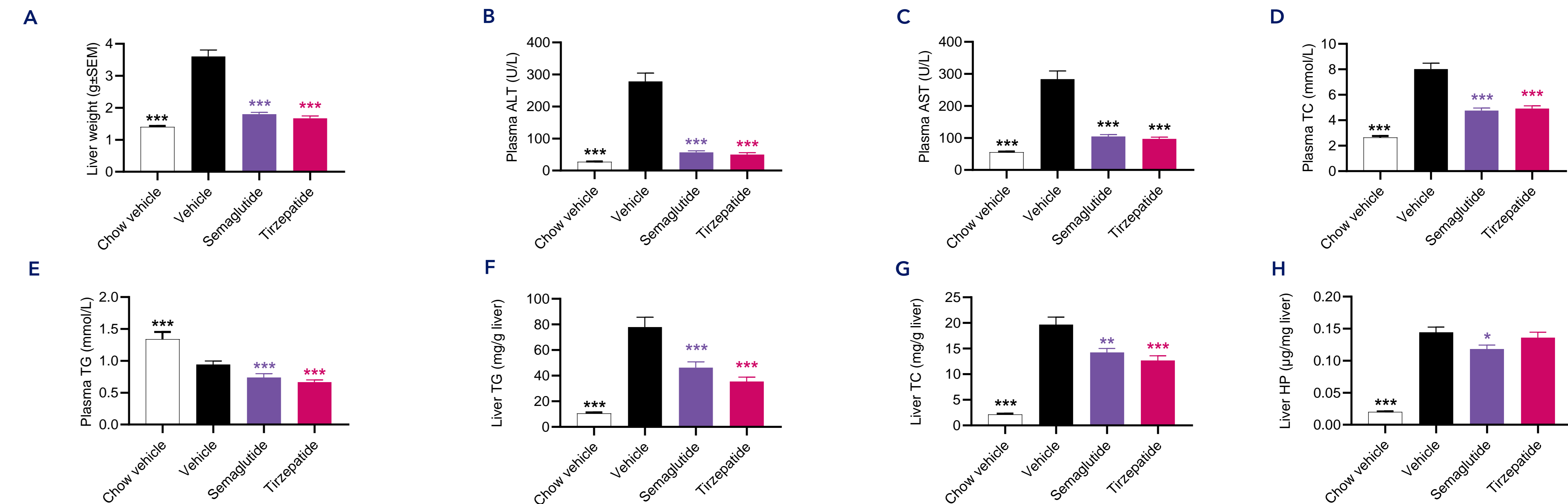


Figure 2. Semaglutide and Tirzepatide treatment reduced liver weight and biochemical parameters (A) Terminal liver weight. (B) Terminal plasma alanine aminotransferase (ALT). (C) Terminal plasma aspartate transaminase (AST). (D) Terminal plasma total cholesterol. (E) Plasma triglycerides (TG). (F) Liver triglycerides (TG). (G) Liver total cholesterol (TC). (H) Liver hydroxyproline (HP). * $p < 0.05$, *** $p < 0.001$ compared to Vehicle. (Dunnett's test one-factor linear model).

3 Body weight and composition

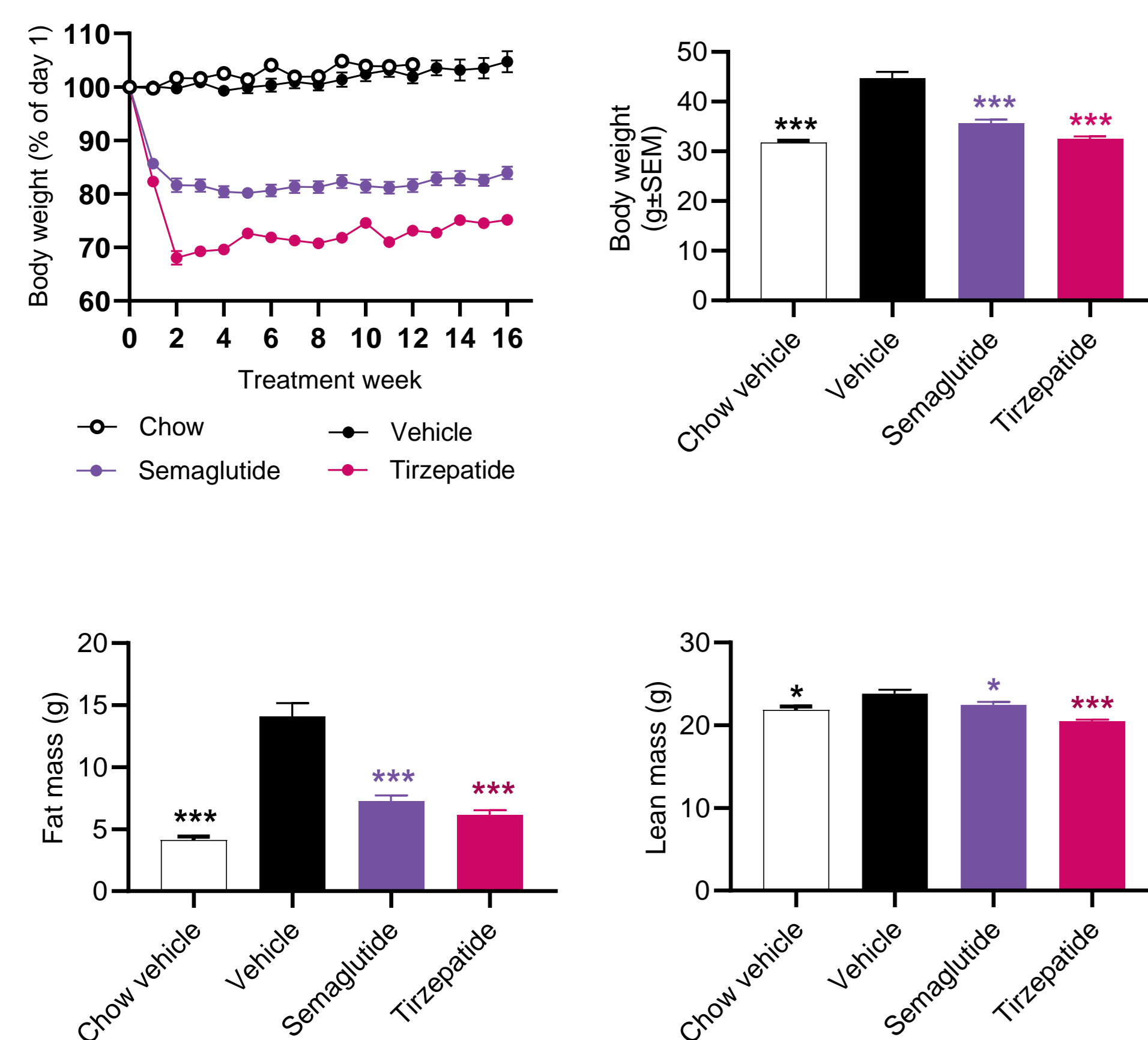


Figure 2. Sustained body weight loss induced by semaglutide and tirzepatide. (A) Relative body weight during study period. (B) Body weight (g). (C) Whole-body fat mass (termination) by echoMRI. (D) Whole-body lean mass (termination) by echoMRI. * $p < 0.05$, *** $p < 0.001$ compared to Vehicle. (Dunnett's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

4 NAFLD Activity Score and Fibrosis Stage

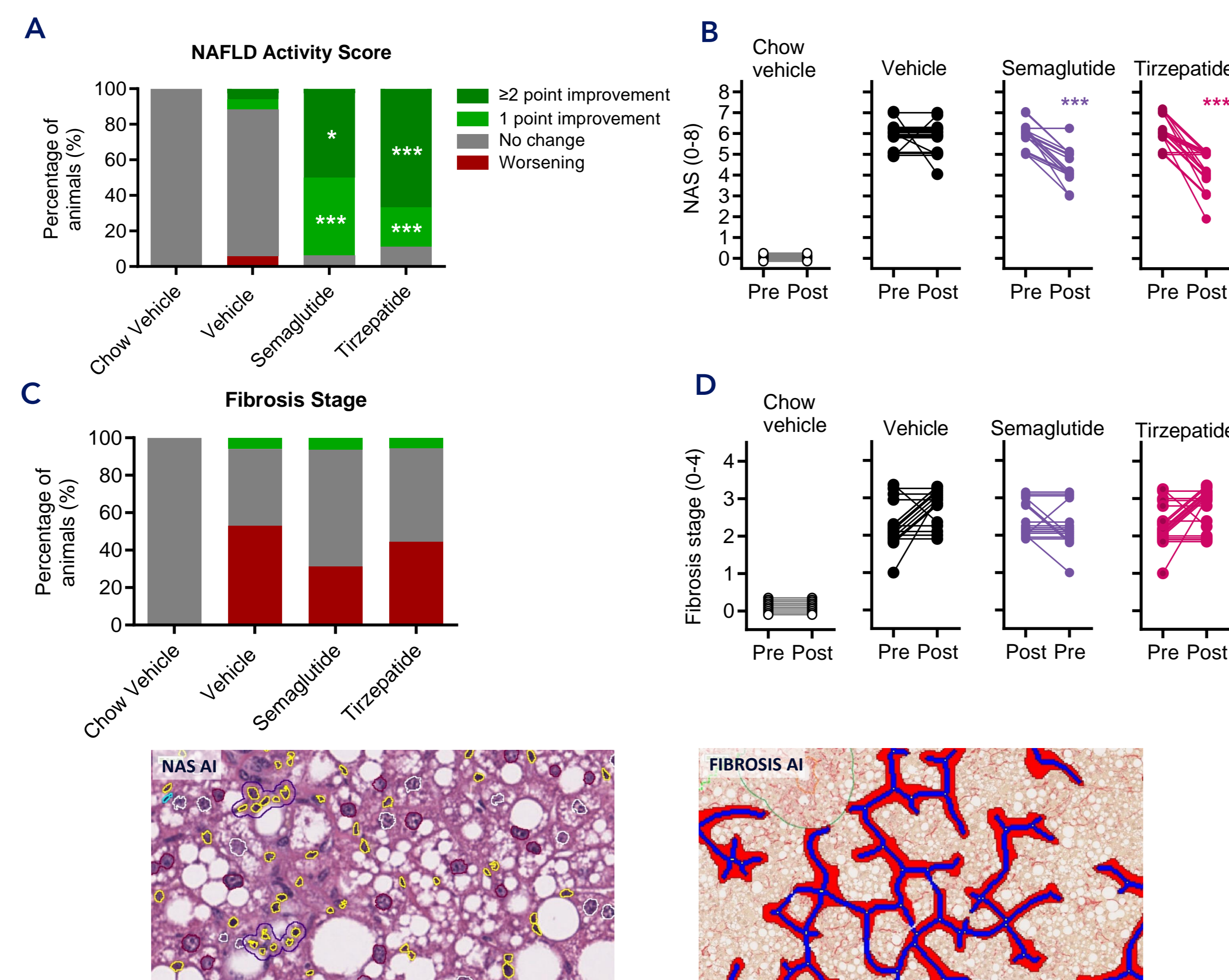


Figure 3. Semaglutide and tirzepatide improve NAFLD Activity Score but not fibrosis stage. Histopathological scores were determined by Gubra Histopathological Objective Scoring Technique (GHOST) deep learning-based image analysis. (A) NAFLD Activity Score (NAS). (B) Individual pre-post NAS. (C) Fibrosis 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 and fibrosis

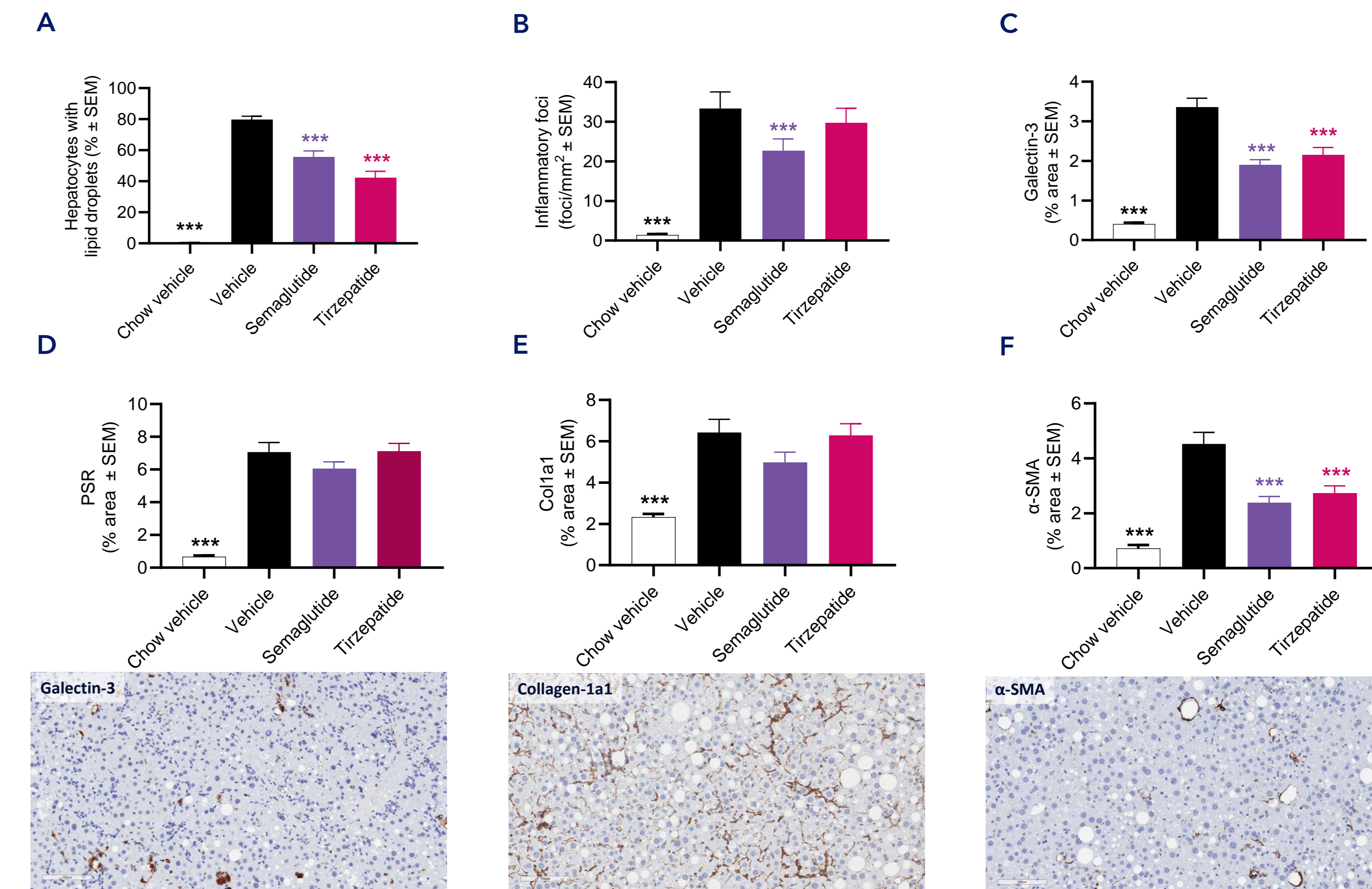


Figure 4. Semaglutide and tirzepatide improve quantitative histological markers of steatosis and inflammation. Histomorphometric assessments were performed by GHOST deep learning-based image analysis on scoring-associated variables (panels A-B) and conventional IHC image analysis (panels C-F). (A) % 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. *** $p < 0.001$ compared to vehicle. Bottom panels: Representative photomicrographs of galectin-3, α -SMA and Col1a1 staining (scale bar, 100 μ m).

Conclusion

- + Semaglutide and tirzepatide induce robust weight loss (17% and 25% respectively) and improve adiposity
- + Both compounds decrease lean mass
- + Semaglutide and tirzepatide improve transaminases, plasma/liver total cholesterol and triglyceride levels
- + Semaglutide and tirzepatide promote 2-point improvement in NAS
- + Benefits on NAS are supported by reduced quantitative histological markers of steatosis and inflammation
- + Semaglutide and tirzepatide shows no effect on fibrosis stage while suppressing fibrogenesis (α -SMA)



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