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

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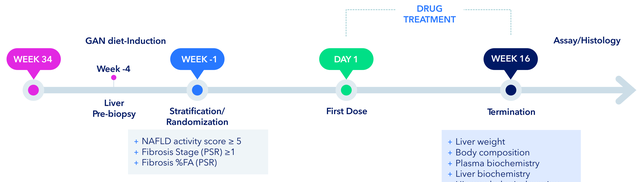
Background & Aim

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



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: SC; subcutaneous, QD; once daily, NA; not applicable, GAN; Gubra Amylin NASH.

2 Body weight and composition

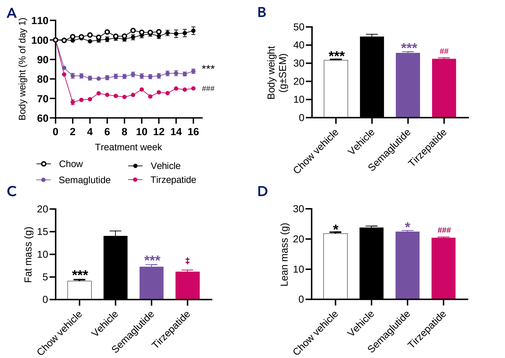


Figure 2. Sustained body weight loss induced by semaglutide and tirzepatide. **(A)** Relative body weight during study period. **(B)** Body weight (g). **(C)** Whole-body fat mass (termination) by echoMRI. **(D)** Whole-body lean mass (termination) by echoMRI.).*p<0.05, ***p<0.001 compared to Vehicle, ### ***p<0.001 compared to semaglutide, ‡ p=0.062 compared to semaglutide. (Dunnett's test one-factor linear model).

3 Metabolic and biochemical parameters

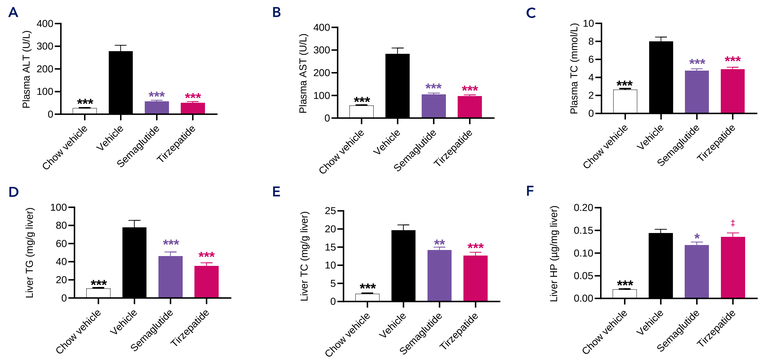
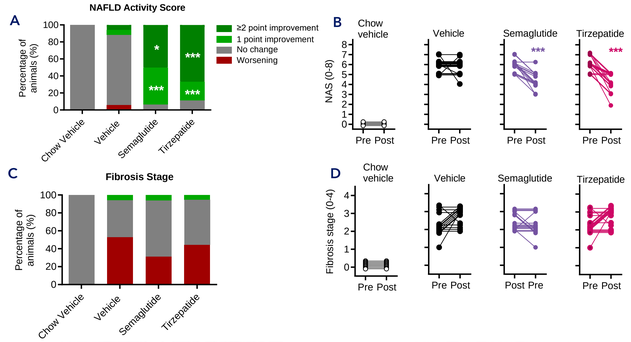


Figure 3. Semaglutide and Tirzepatide treatment reduced liver weight and biochemical parameters (A) Terminal liver weight. **(B)** Terminal plasma alanine aminotransferase (ALT). **(C)** Terminal plasma aspartate transaminase (AST). **(D)** Terminal plasma total cholesterol.**(E)** Liver triglycerides (TG). **(F)** Liver hydroxyproline (HP). *p<0.05, ***p<0.001, ‡ p=0.0705 compared to Vehicle. (Dunnett's test one-factor linear model).

4 NAFLD Activity Score and Fibrosis Stage



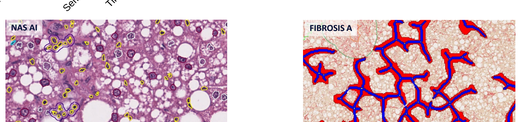
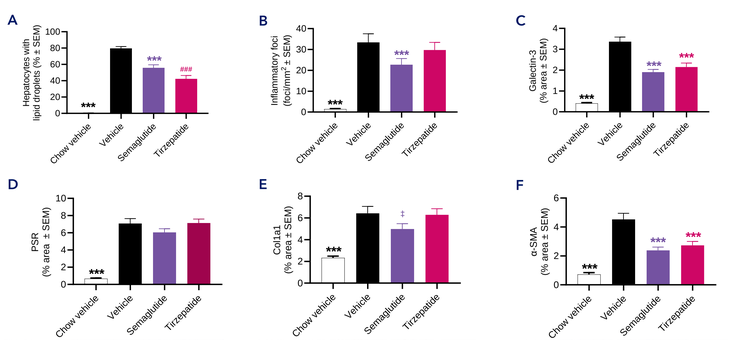
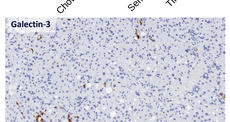
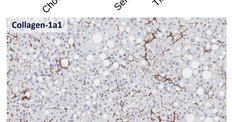


Figure 4. Semaglutide and tirzepatide improve NAFLD Activity Score but not fibrosis stage. Histopathological scores were determined by Gubra Histopathological Objective Scoring Technique (GHOST) deep learning-based image analysis. **(A)** NAFLD Activity Score (NAS). **(B)** Individual pre-post NAS. **(C)** 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







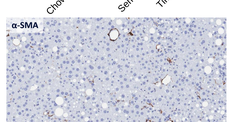
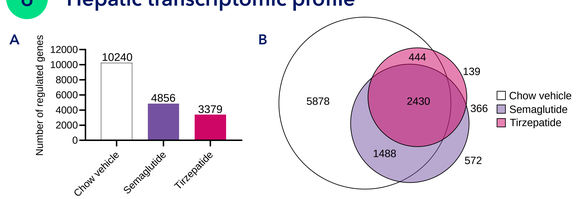


Figure 5. Semaglutide and tirzepatide improve quantitative histological markers of steatosis and inflammation. Histomorphometric assessments were performed by GHOST deep learning-based image analysis on scoring-associated variables (panels A-B) and conventional IHC image analysis (panels C-F). **(A)** % 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 ± SEM. ***p<0.001 compared to vehicle, ‡ p=0.0871 compared to vehicle, ### p<0.001 compared to semaglutide. Bottom panels: Representative photomicrographs of galectin-3, α-SMA and Col1a1 staining (scale bar, 100 µm).

6 Hepatic transcriptomic profile



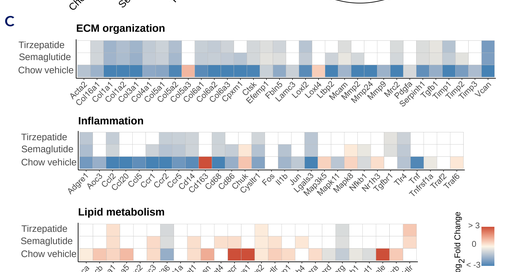


Figure 6. Semaglutide and tirzepatide affect number of differentially expressed genes (A) Differentially expressed genes. **(B)** Gene regulation overlap. **(C)** Changes in candidate gene expression markers of extracellular matrix (ECM), inflammation and lipid metabolism (log2-fold change compared to 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% respectably) 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)
- Semaglutide and tirzepatide induces a similar hepatic transcriptome profile

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