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The GLP-1 receptor agonist semaglutide improves hepatic steatosis, inflammation and fibrosis in a dietary mouse model of Nonalcoholic fatty liver disease (NAFLD)/nonalcoholic steatohepatitis (NASH).

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Background:
Nonalcoholic fatty liver disease (NAFLD) is a common complication of obesity and type 2 diabetes (T2D). NAFLD affects up to 90% of obese individuals and 60% of diabetic patients. NAFLD can progress to nonalcoholic steatohepatitis (NASH) which can itself lead to cirrhosis and hepatocellular carcinoma. Despite the high prevalence of the disease no pharmacologic treatments are presently approved. As GLP-1 receptor agonists (GLP-1 RAs) are now widely used in the treatment of T2D, our study aimed to assess their potential beneficial effects on NAFLD/NASH.

Methods:
Wild-type C57BL/6J male mice were fed a chow or a choline-deficient, L-amino acid-defined, high-fat diet (CDAHFD) to induce NAFLD/NASH. After 3 weeks on CDAHFD diet, mice were subcutaneously infused with either semaglutide (3.5 µg/d) or saline solution for 3 weeks using osmotic minipumps before post-mortem analysis. Liver tissues were studied using qPCR, RNA sequencing (RNAseq), histological stainings (oil red O/Sirius red) and fluorescence-activated cell sorting (FACS) analysis.

Results:
CDAHFD consumption results in NAFLD/NASH onset in mice. Semaglutide-infused mice presented reduced body and liver weights compared to controls. Histological analysis revealed a significant decrease in hepatic steatosis and fibrosis in the semaglutide-infused mice. Semaglutide treatment was associated with a significant decrease in Alanine transaminase (ALT) and a significant increase in High-Density Lipoprotein (HDL) levels in blood compared to saline controls. A downexpression of genes involved in fibrogenesis (Tgfb1, Timp1, Col1a1), inflammatory status (Il1b, Il6, Il12, Tnfa) and recrutment of blood-derived macrophages (Ly6c, Ccr2) was also observed in the liver of semaglutide-treated mice. Gene set enrichment analysis of hepatic transcriptomes confirm that the administration of semaglutide dampens the overexpression of pro-inflammatory, pro-fibrotic and oxidative stress markers associated with dietary NAFLD/NASH. In addition, analysis of liver cell composition by FACS revealed a decrease in Th1-type immune response in semaglutide-treated mice compared to controls.

Conclusion:
The long-acting GLP-1 RA semaglutide reduces liver steatosis, inflammation and fibrosis in a dietary mouse model of NAFLD/NASH. These results suggest additive beneficial actions of semaglutide regarding NAFLD/NASH progression, in addition to its well known glucose-lowering action.