

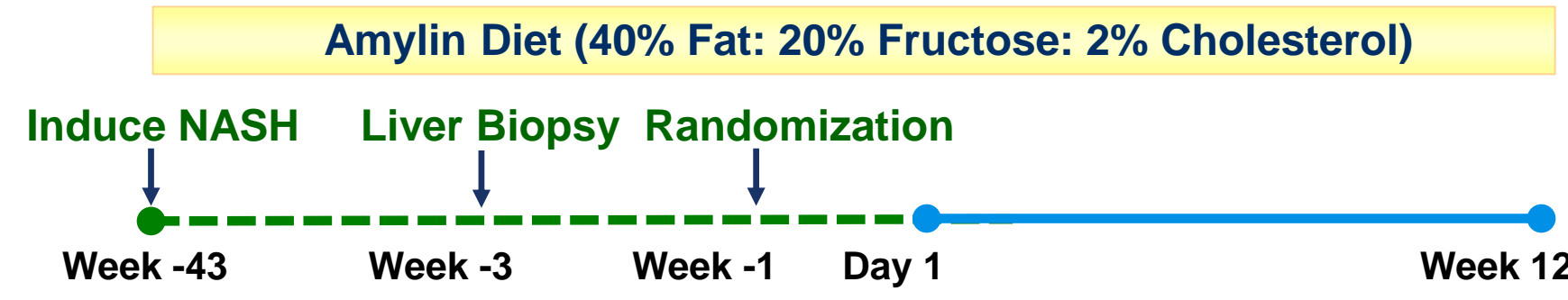
Efficacy of Seladelpar for Amelioration of Fibrosis and NASH in a Diet-Induced and Biopsy-Confirmed Mouse Model: Comparison to Liraglutide, Selonsertib and Obeticholic Acid

BACKGROUND

Non-alcoholic steatohepatitis (NASH) is increasingly the cause of cirrhosis, hepatocellular carcinoma and the need for liver transplantation. Numerous therapies are being evaluated in clinical trials. However, there are currently no approved treatments for NASH. Seladelpar is a potent and orally active PPAR δ agonist, which is presently in a phase 2b clinical trial for the treatment of NASH. Here we compare the activity of seladelpar to liraglutide, obeticholic acid (OCA) and selonsertib, three potential therapies for NASH, in a diet-induced and biopsy-confirmed mouse model of NASH.

METHODS

Male C57BL/6J mice were fed a diet high in fat, fructose and cholesterol for 43 weeks. Prior to treatment, mice with histologically confirmed steatosis (score ≥ 2) and fibrosis (stage ≥ 1) were randomized into groups and then treated daily for 12 weeks. Lipids and transaminases were measured. Liver pathology was evaluated by H&E staining, NAS scores and quantitative morphometry. Palmitate-induced mitochondrial fatty acid oxidation (oxygen consumption rate: OCR) was measured in cultured HepG2 cells using a Seahorse system. Liver fibrosis was assessed by fibrosis stage, hydroxyproline levels and histomorphometric analysis.



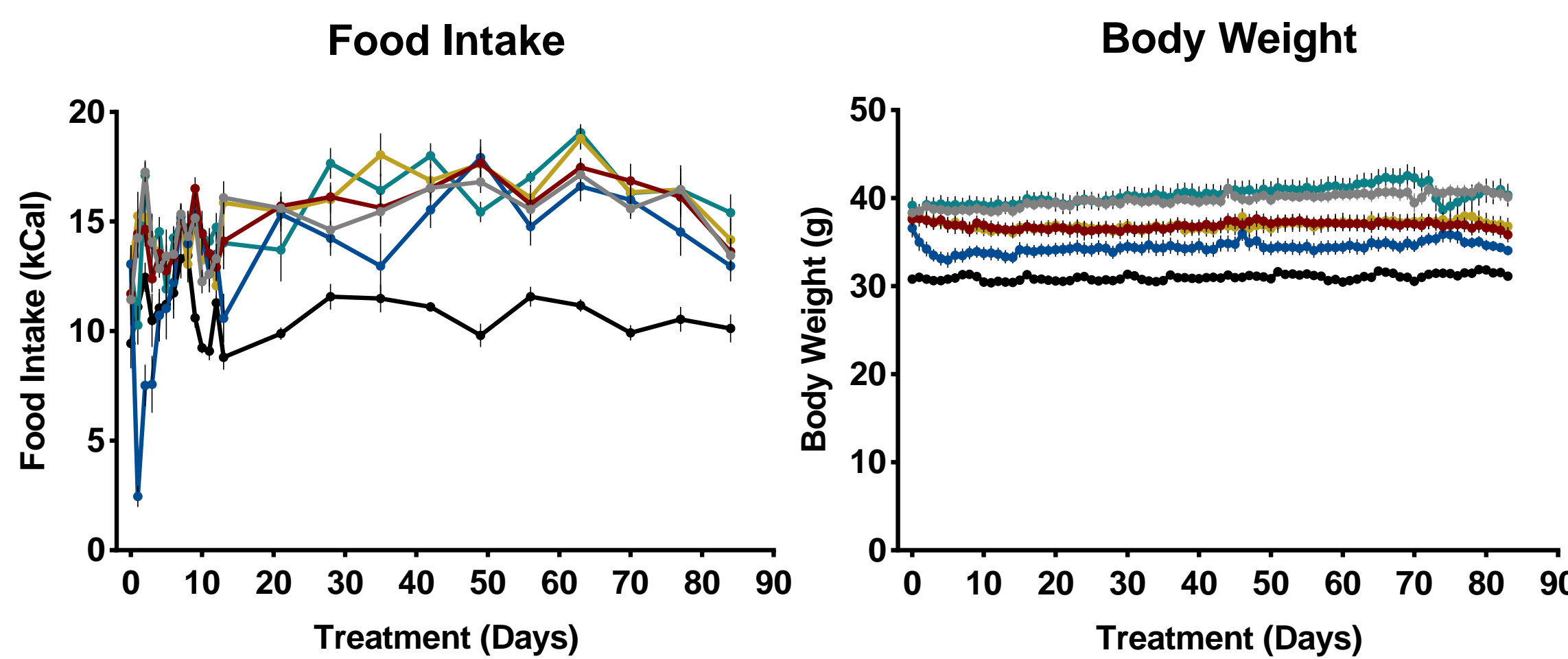
Treatment Groups

- NASH Vehicle
- Seladelpar (10 mg/kg, QD, PO)
- Liraglutide (0.4 mg/kg, BID, SC)
- Selonsertib (30 mg/kg, BID, PO)
- OCA (30 mg/kg, QD, PO)
- CHOW Vehicle

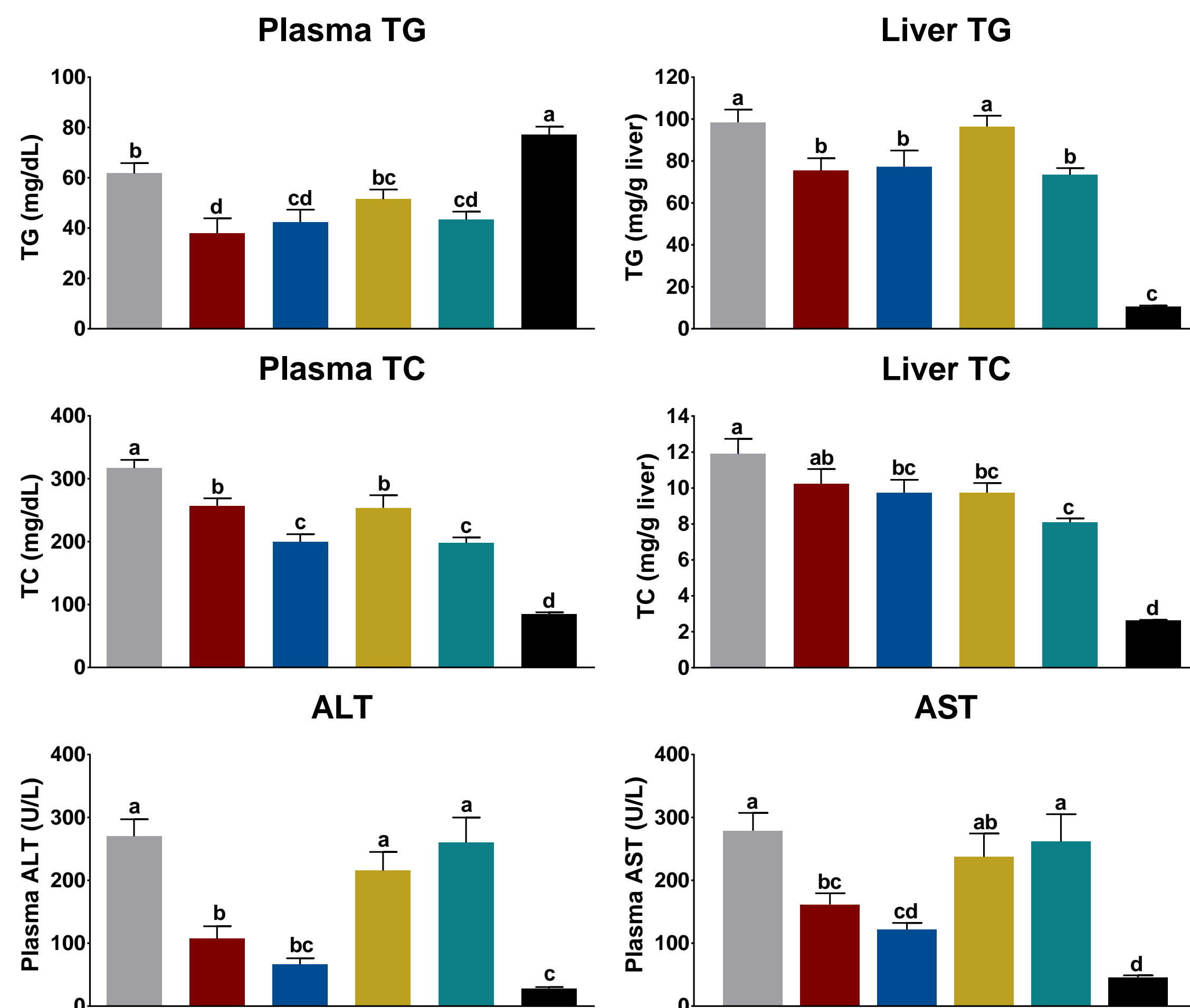
Data are presented as Mean \pm SE; P-values: * < 0.05; ** < 0.01; *** < 0.001; **** < 0.0001
Statistical significance (P-value < 0.05) between groups are presented by different letters

RESULTS

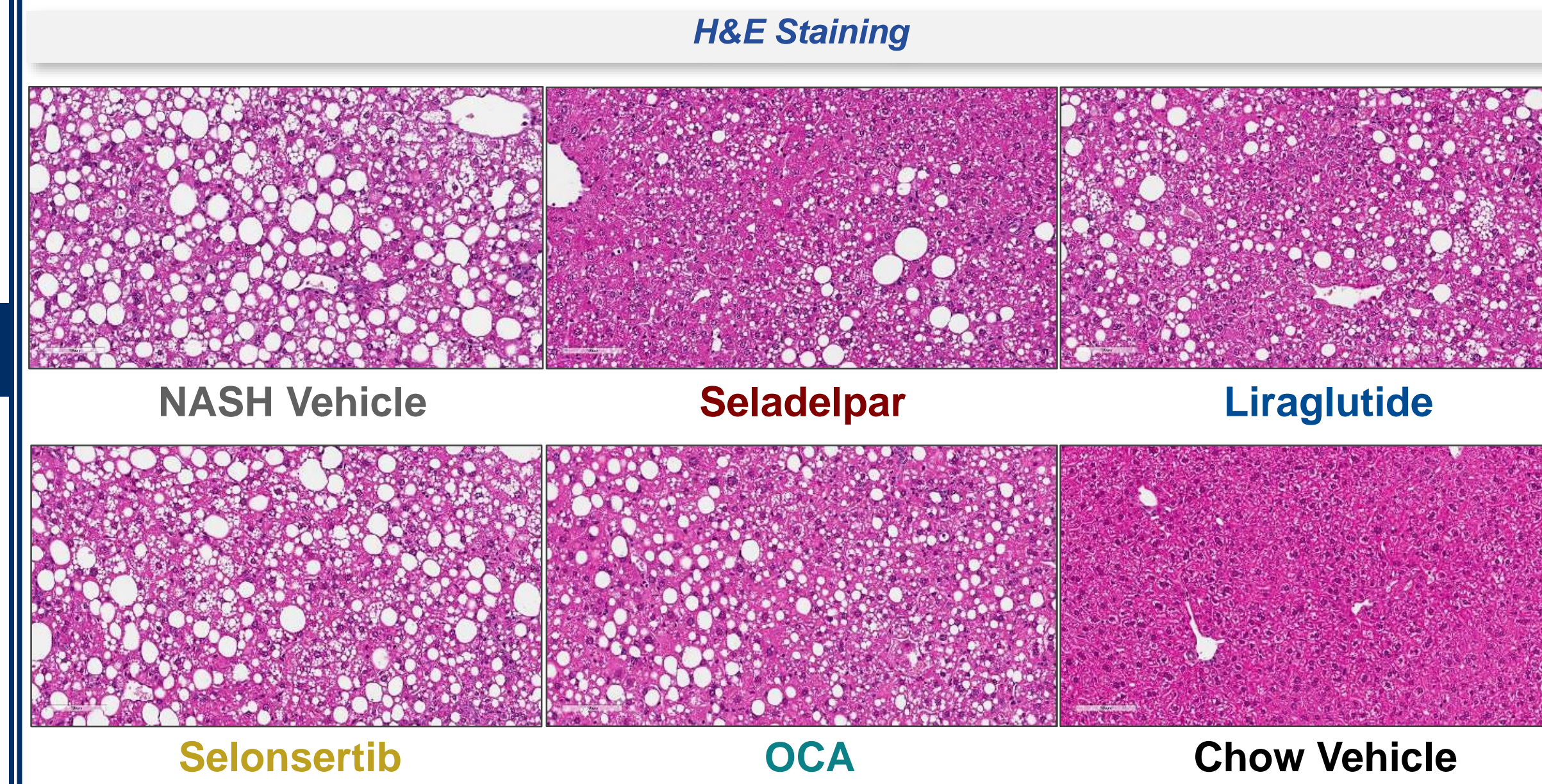
Food Intake & Body Weight



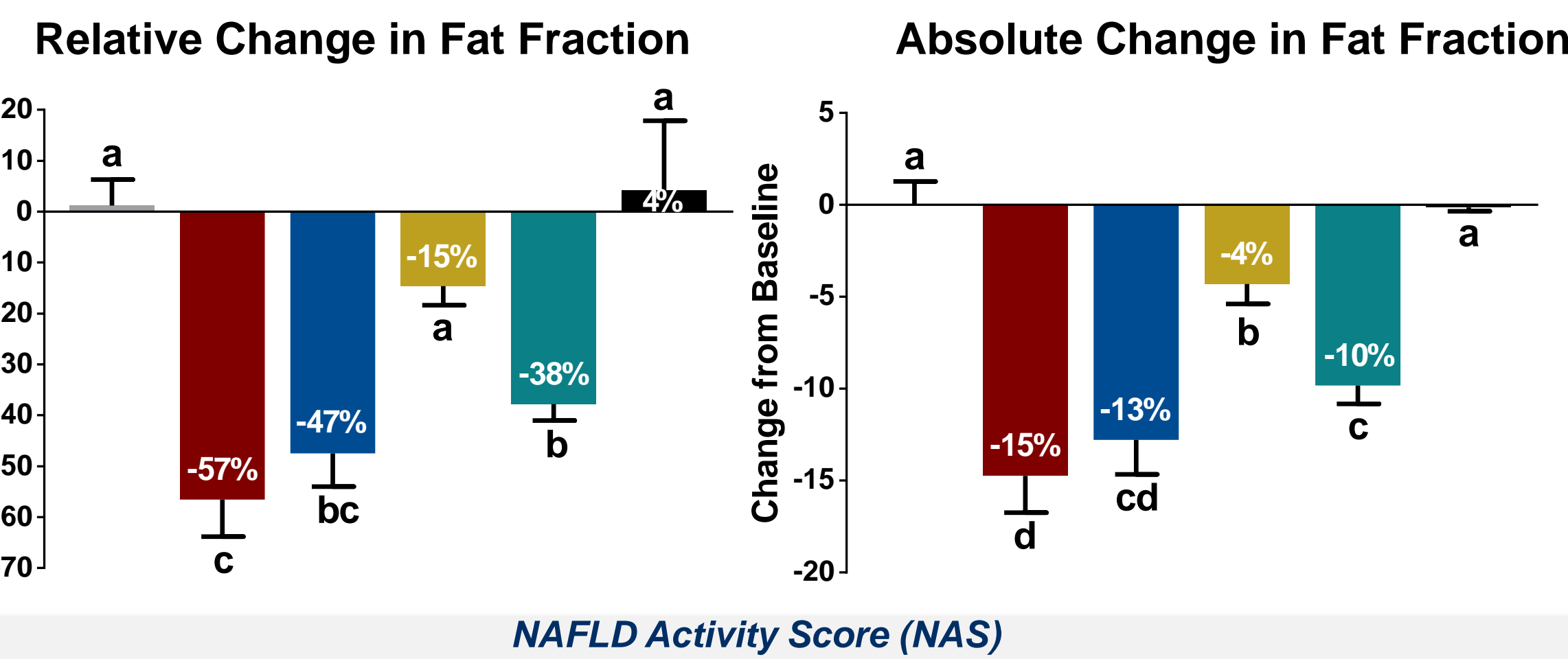
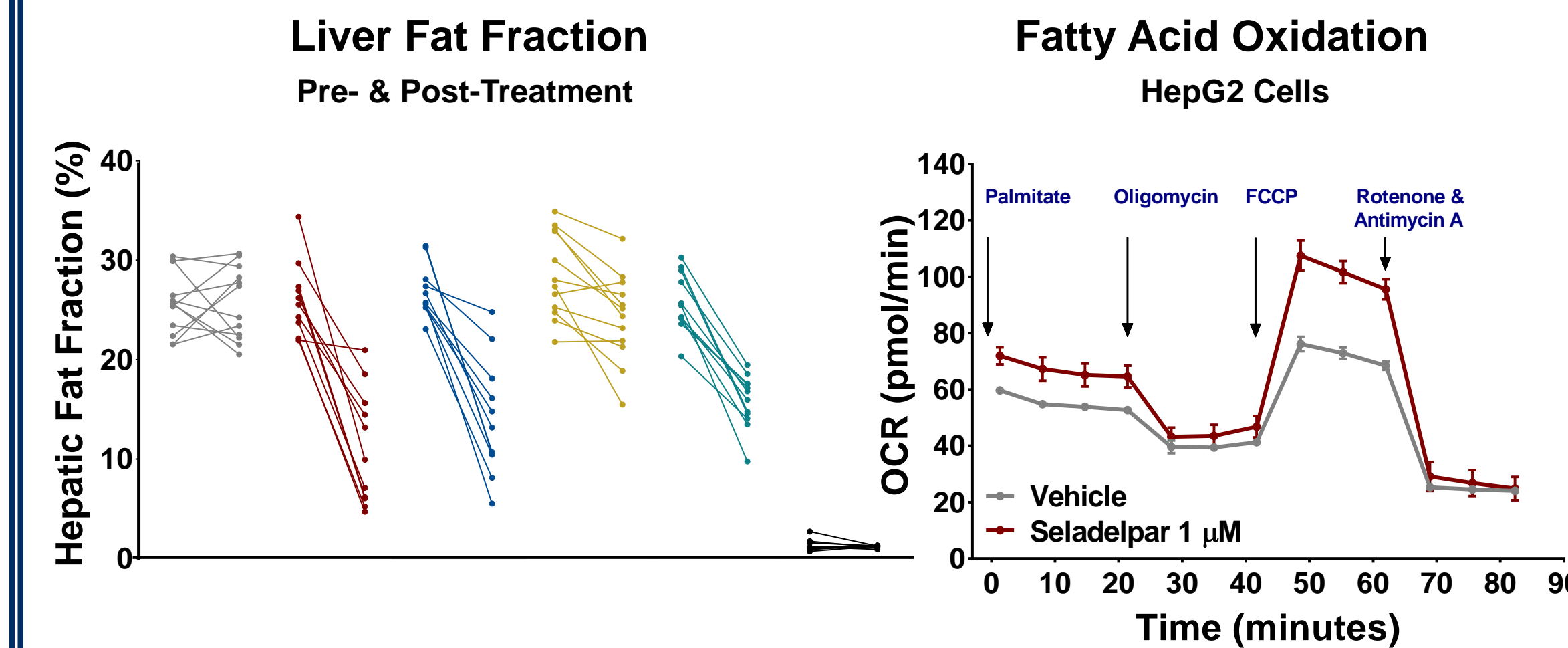
Lipids & Liver Enzymes



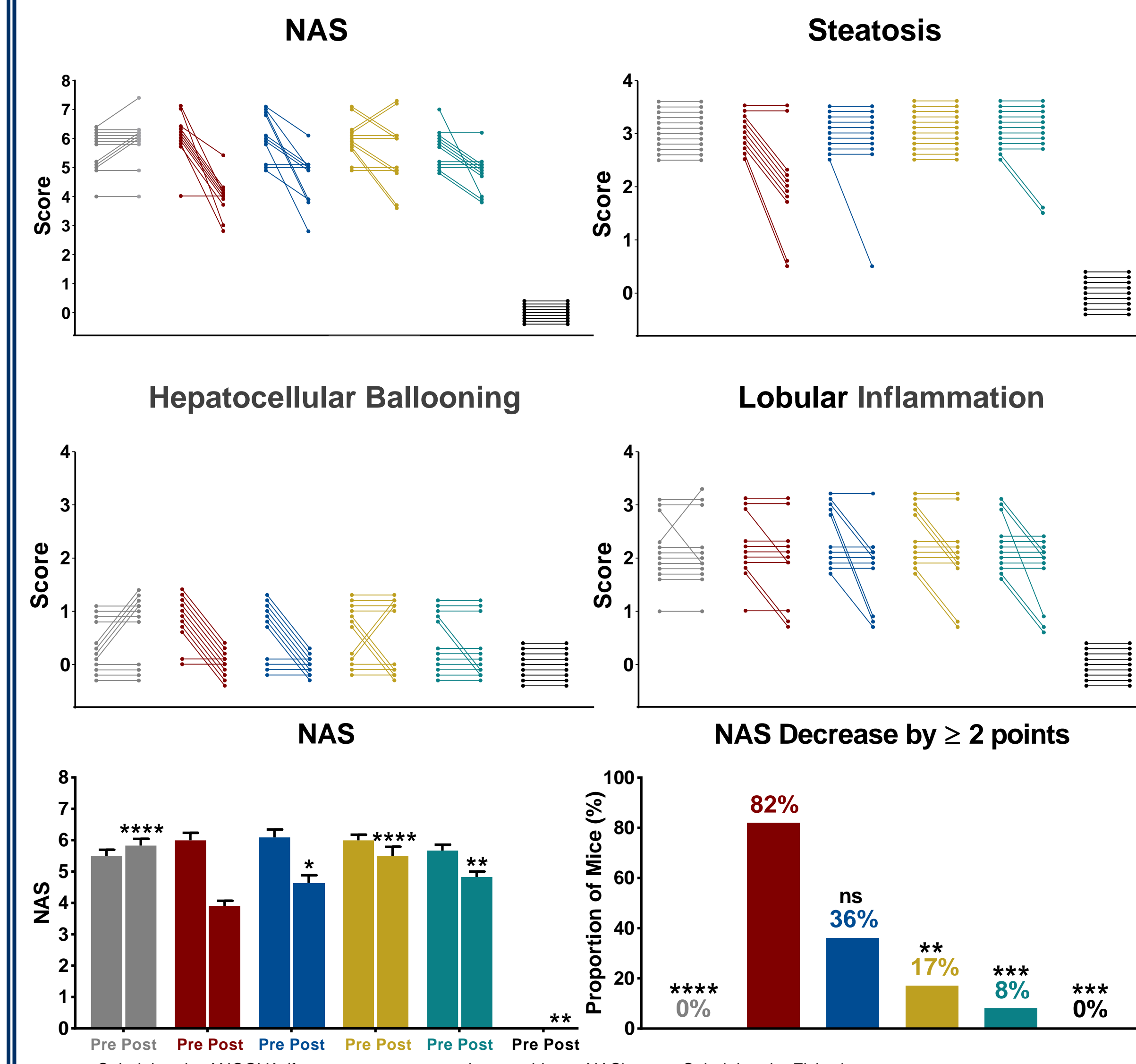
Liver Steatosis



Liver Fat by Morphometric Analysis

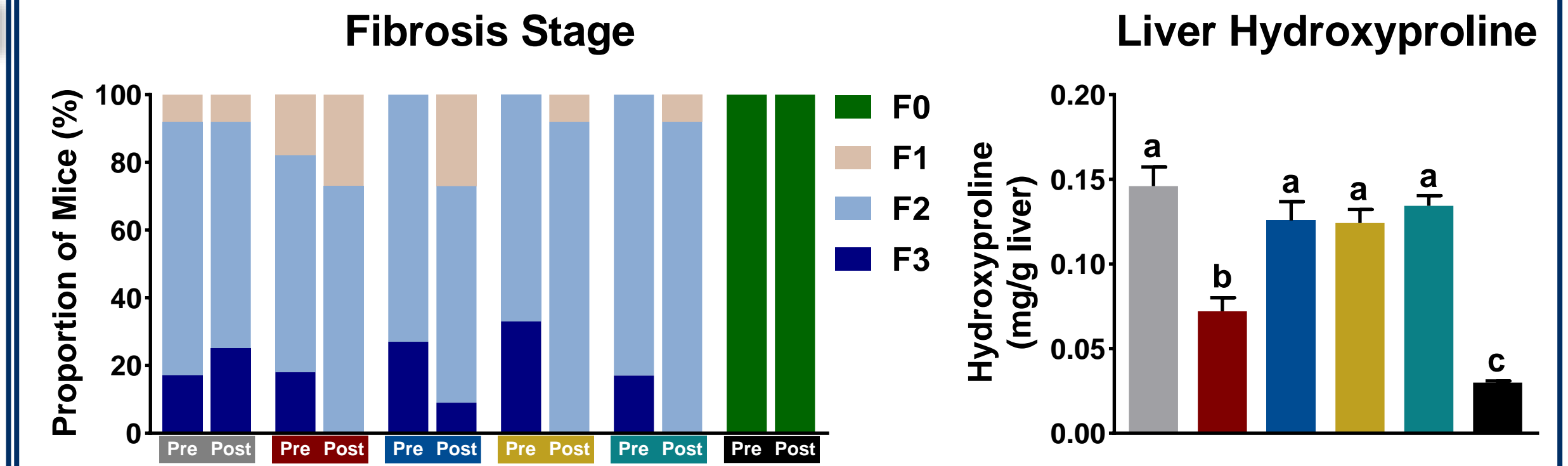


NAFLD Activity Score (NAS)

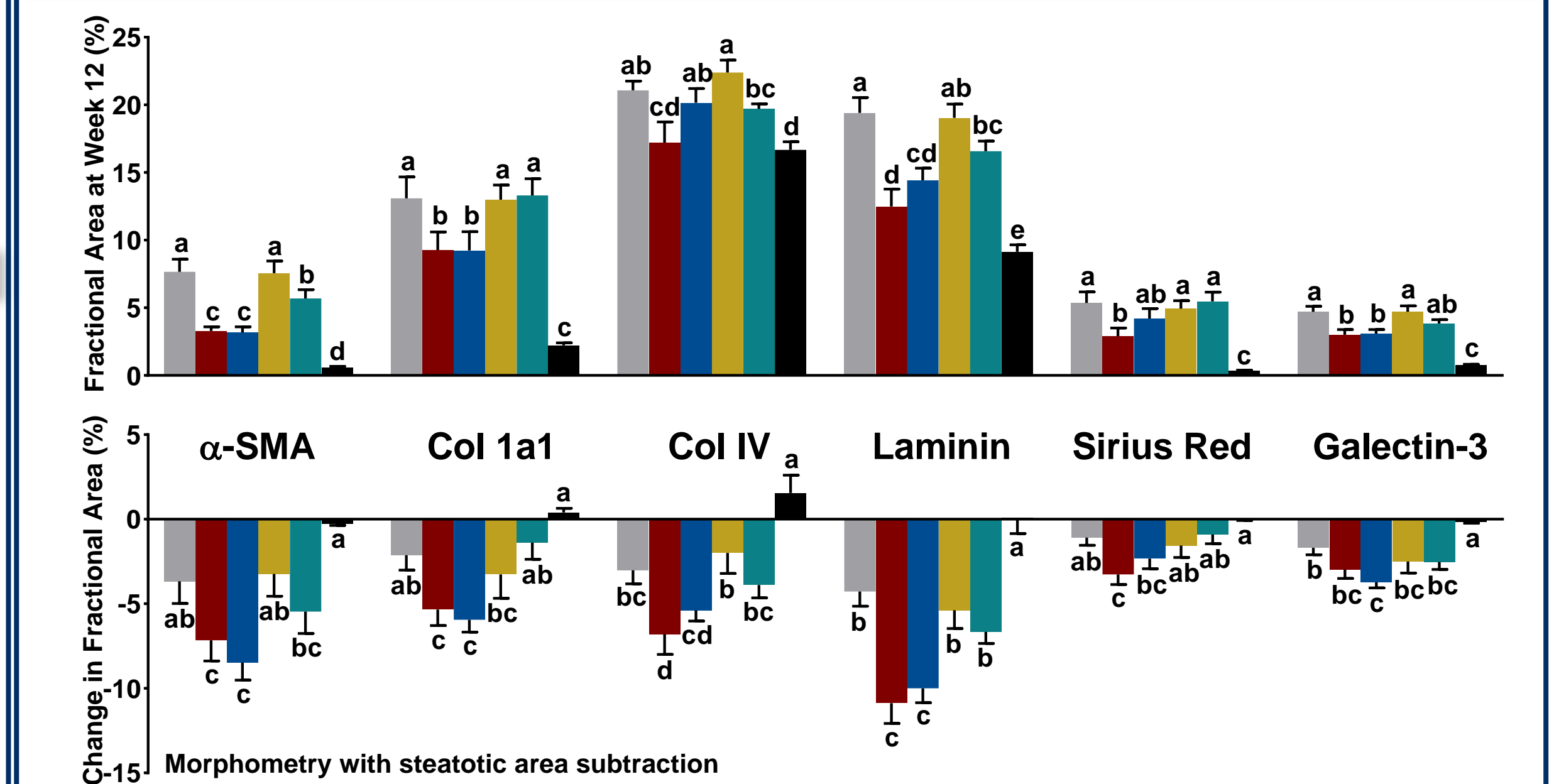


RESULTS

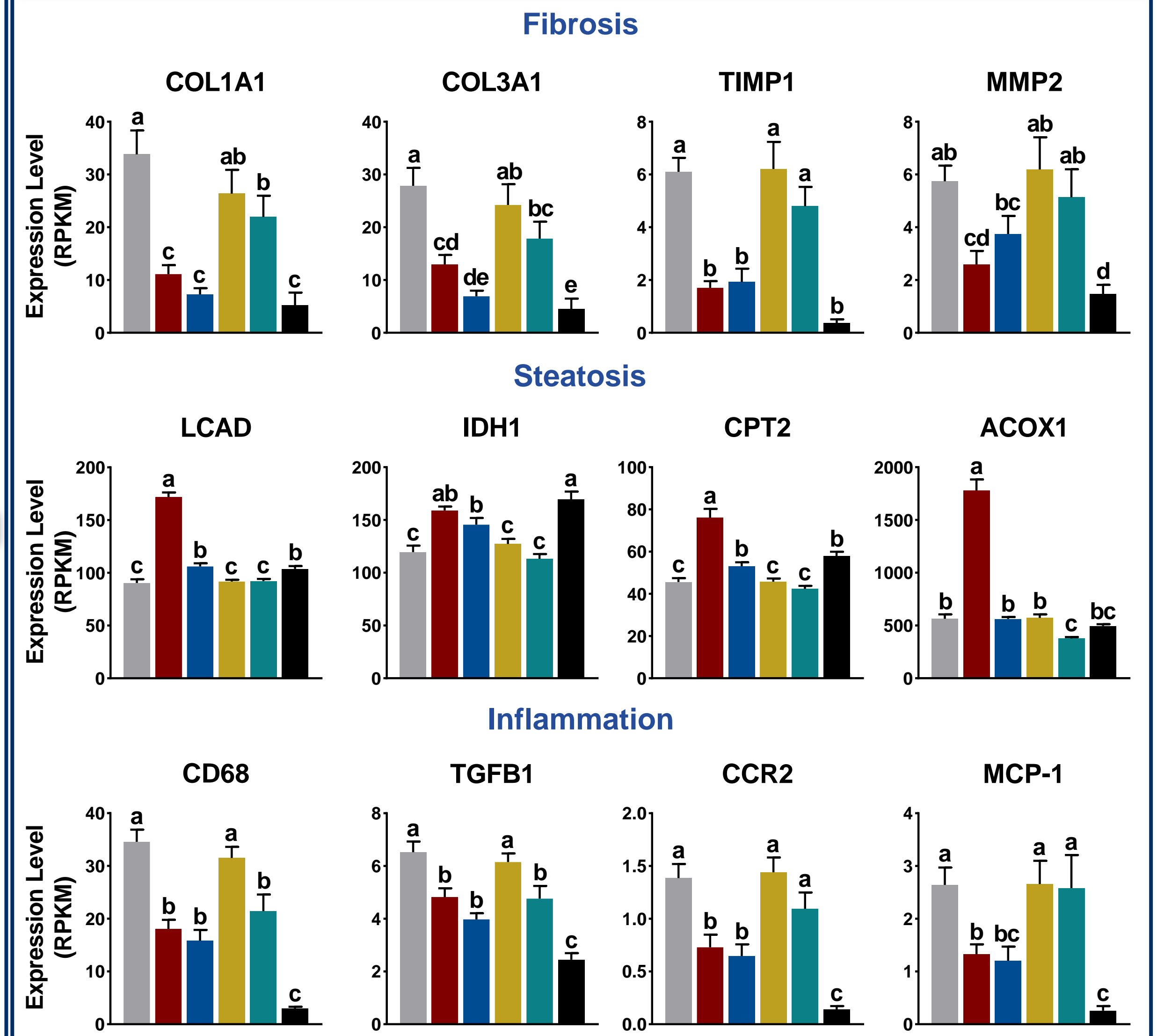
Liver Fibrosis & Inflammation



Liver Fibrosis by Morphometric Analysis



RNAseq Analysis



CONCLUSION

Seladelpar treatment for 12 weeks in a diet-induced obesity mouse model of NASH:

- Most pronounced effect on decrease of hepatic fat fraction
- Decreased NAS
 - Improved steatosis score
 - Achieved complete resolution of hepatocellular ballooning
 - Reduced inflammation
- Resolved established bridging fibrosis
- Decreased liver collagen content as evidenced by hydroxyproline, histological staining and gene expression
- The most pronounced overall effect for reducing fibrotic markers

Phase 2b NASH study is ongoing
NCT03551522