Treatment of Nonalcoholic fatty liver disease (NAFLD) constitutes an unmet clinical need owing to the relatively limited efficacy of both novel and readily available metabolic medications, thus warranting pathobiological investigations on the mechanisms of single or combination regimens. In this context, our study aimed to assess and compare whether and how liraglutide, a glucagon-like peptide-1 receptor agonist, and elafibranor, a dual peroxisome proliferator-activated receptor alpha-delta agonist, may affect hepatic histology and metabolipidomic fingerprints in a model of advanced NAFLD. Male C57BL/6JRj mice with biopsy-confirmed hepatosteatosis and fibrosis induced by AMLN diet (40% fat with 20% trans-fat, 2% cholesterol and 22% fructose) were randomized to receive for 12 weeks: a) Liraglutide (0.4 mg/kg/d s.c.), b) Elafibranor (30 mg/kg/d p.o.), c) vehicle. Metabolic indices, liver function markers, liver pathology, and metabolomics/lipidomics were assessed at study completion. Both drugs markedly reduced body weight and fat percentage (p-value <0.001), and improved glucose tolerance and insulin sensitivity, as indicated by oral glucose and intraperitoneal insulin tolerance tests. Hepatic lipid content was downregulated under both treatments (p-value <0.001), especially under elafibranor, which also elevated liver weight in contrast with liraglutide (p-value vs liraglutide <0.001). NAFLD activity score (pre-to-post) and its histological components were substantially improved (mean difference ± standard error of mean: -1.4 ± 0.3 for liraglutide; -2.0 ± 0.2 for elafibranor), with elafibranor demonstrating a more robust anti-steatotic effect vs liralgutide (p-value <0.01) as well as anti-fibrotic effects (-0.5 ± 0.1). Liraglutide also limited the immunohistochemical expression of pro-inflammatory markers of Kupffer and hepatic stellate cell function (Galectin-3, Collagen type I alpha 1, and alpha-smooth muscle actin). In the omics analysis, elafibranor profoundly ameliorated the hepatic lipidome by diminishing the concentrations of glyceride species, increasing phospholipids and carnitine metabolites, and modifying key regulators of fatty acid oxidation, inflammation, and oxidative stress, including metabolites of methionine, glutathione, and pantothenate. Liraglutide significantly affected bile acid and carbohydrate metabolism by restoring the concentrations of metabolically beneficial primary and secondary bile acids, glycogen metabolism by-products, and pentoses, thus probably driving glycogen utilization-turnover and nucleic acid synthesis. Thus, liraglutide and elafibranor diverge in their mechanistic treatment of advanced NAFLD pathology, indicated by their robust but differential regulation of the hepatic metabolipidome. These findings support their combinatory therapeutic evaluation in future studies.

# Cardiovascular Endocrinology

## LIPIDS AND STEROIDS IN CARDIOVASCULAR DISEASE

### *Genome-Wide Meta-Analysis and Mendelian Randomization Identify Early Biomarkers of Non-Alcoholic Fatty Liver Disease*

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**Background:** The diagnosis of non-alcoholic fatty liver disease (NAFLD) is often challenging. Blood-based biomarkers which are causally influenced by NAFLD and that are not modulated by secondary non-causal pathways, are promising candidates for the identification of patients with NAFLD. **Objectives:** To identify blood metabolites and blood proteins that are causally impacted by the presence of NAFLD using Mendelian randomization (MR). **Methods:** We created a NAFLD genetic instrument through the identification of independent single-nucleotide polymorphisms associated with NAFLD in a meta-analysis of genome-wide association studies (GWAS) (6715 cases and 682,748 controls). Using inverse-variance weighted MR, we investigated the impact of NAFLD on 123 blood metabolites (in 24,925 participants from 10 European cohorts) and 3283 blood proteins (in 3301 participants from the INTERVAL cohort). **Results:** Our genetic instrument for genetically predicted NAFLD included 12 SNPs at the *MTARC1*, *GCKR*, *LPL*, *TRIB1*, *LMO3*, *FTO*, *TM6SF2*, *APOE* and *PNPLA3* loci. After correction for false-discovery rate, we found a positive effect of NAFLD on blood tyrosine levels and on blood levels of eight proteins (encoded by the *IDUA*, *ADH4*, *HMGCS1*, *GSTA1*, *ASL*, *POR*, *FBP1* and *CTSZ* genes). These association were robust to outliers and we found to evidence of horizontal pleiotropy. **Conclusions:** We report the existence of a potentially causal impact of the presence of NAFLD on tyrosine metabolism as well as on eight circulating proteins, which could potentially represent early biomarkers of NAFLD.

# Cardiovascular Endocrinology

## LIPIDS AND STEROIDS IN CARDIOVASCULAR DISEASE

### *Leptin Improves Cardiac Structure and Function in Patients With Generalized Lipodystrophy*

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Lipodystrophy (LD) syndromes are rare disorders of deficient adipose tissue and severe metabolic disease, including insulin resistance, diabetes, and hypertriglyceridemia. LD may affect all adipose depots (generalized LD, GLD) or only some depots (partial LD, PLD). Low adipose mass leads to very low leptin in GLD, and variable leptin in PL. Treatment with exogenous leptin (metreleptin) improves metabolic disease in LD, particularly GLD. Left ventricular (LV) hypertrophy is frequent in LD, especially GLD. The mechanism for hypertrophy in LD is not known and may relate to glucose or lipotoxicity. We hypothesized that metreleptin would improve cardiac abnormalities in LD, and that this would be mediated by improvements in glucose and triglycerides (TG). We analyzed echocardiograms (echo), blood pressure (BP), heart rate (HR), and metabolic