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steatohepatitis (NASH). Proprotein convertase subtilisin/kenin type 9 (PCSK9) is secreted into the plasma by the liver and regulates lipid homeostasis by promoting degradation of the LDL receptor and possibly lipogenesis, disrupting cholesterol homeostasis. The aim of the study was to examine the effect of hepatic steatosis on circulating PCSK9 levels.

Methods: 64 NAFLD biopsy-proven patients were recruited at the Virgen del Rocío University Hospital. Patients were classified by SAF score as SS (n=24) or NASH (n=40). Levels of circulating PCSK9 were evaluated by ELISA.

Results: Mean age was 48±15 and 54±10 in the SS and NASH group respectively (p=0.04). Levels of triglycerides were significantly higher in NASH (180.4±81.2 vs. 114.7±56.2; p=0.001). HDL cholesterol were higher in SS than in NASH patients (60±23 vs. 41.2±10.3; p<0.001) while levels of LDL cholesterol and total cholesterol were similar between both groups (0.385 and 0.225 respectively). PCSK9 in NASH patients was significantly higher (p<0.001). Patients without inflammation (n=6; 9.8%) had lower levels of PCSK9, than those with mild (n=29, 47.5%) or moderate grade of inflammation (n=16; 26.2%) (p=0.014). Indeed, PCSK9 was lower in patients without ballooning (n=21, 42%) than in those with mild (n=24; 48%) or significant ballooning (n=5; 20.8%) (p=0.001).

Conclusions: Circulating PCSK9 levels correlated positively with ballooning and inflammation degree in NAFLD patients. Modulation of PCSK9 synthesis and release might be involved in NAFLD pathogenesis. PCSK9 could be a link between advanced NAFLD and cardiovascular risk.

P267 / #1006, E-POSTERS TOPIC: 2. LIPIDS AND LIPOPROTEINS / 2.11 LIVER METABOLISM AND STEATOSIS

DOWNREGULATION OF INTERLEUKIN 32 REDUCE INTRACELLULAR TRIGLYCERIDE LEVELS IN LIVER SPHEROIDS

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Background and Aims: Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease worldwide, and currently there are no approved drugs for treatment. Rationale: We have shown Interleukin 32 (IL32) is upregulated in the liver of individuals at risk for NAFLD.

Methods: We used in vitro cultured hepatocytes and 3D spheroids derived from immortalized hepatocytes and hepatic stellate cells, to understand the mechanisms through which IL32 affects lipid metabolism.

Results: We observed increase in intracellular triglyceride content after incubation with human recombinant IL32β. Downregulation of endogenous IL32 expression reduced intracellular triglyceride content, de novo triglyceride synthesis, and apolipoprotein B (APOB) synthesis and secretion. RNA-Seq derived data from the livers of individuals with NAFLD and from our 3D spheroids revealed that downregulation of IL32 resulted in reduced hepatic lipid metabolism.

Conclusions: In our model, IL32 reduces intracellular triglyceride content by reducing de novo triglyceride synthesis. Impact: IL32 has tremendous potential against NAFLD and may be a future therapeutic target against this disease.

P268 / #1038, E-POSTERS TOPIC: 2. LIPIDS AND LIPOPROTEINS / 2.11 LIVER METABOLISM AND STEATOSIS

LIVER-HUMANIZED MICE FED A NASH-DIET ARE AN ADVANCED MODEL TO STUDY CARDIOMETABOLIC DISEASES

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Background and Aims: Conventional mouse models of diet-induced cardiometabolic diseases, e.g., atherosclerosis and nonalcoholic steatohepatitis (NASH), are limited to recapitulate the full pathology of human disease. Conversely, dietary challenge in liver-humanized mice (LHM), i.e., mice repopulated with human hepatocytes, can be more relevant to study cardiometabolic diseases as LHM exhibit a human-like lipoprotein and liver lipid metabolism. Nevertheless, we have previously reported LHM to be resistant to high-fat/high-sucrose diet. Here, we aimed to investigate whether LHM developed cardiometabolic diseases when challenged with a high-fat/high-fructose/high-cholesterol diet (NASH-diet).

Methods: Immune-deficient FRG mice receiving hepatocytes from one human donor or NOD mouse (liver-murinized mice, LMM) were fed a NASH-diet for 8, 12, 16 or 20 weeks. Plasma lipids and APOB were quantified by routine clinical assays. Cholesterol was analyzed from Folch extracts of the descending aorta by GC-MS. Histology analysis on embedded heart or liver was performed by staining with hematoxylin and eosin, Oil Red O, or anti-mouse CD68-antibody conjugate.

Results: LHM exhibited higher levels of plasma remnant- and LDL-cholesterol, triglycerides and APOB compared with LMM, which instead had higher levels of HDL-cholesterol. LHM had also higher levels of cholesterol esters accumulated within the aorta. Heart histology revealed accumulation of lipids (wk 8-20) and CD68-positive cells (wk 8-12) in the aortic valves. Similarly, liver histology showed hepatocyte steatosis (wk 8), ballooning and fibrosis (wk 12).

Conclusions: LHM fed a NASH-diet rapidly exhibited time-dependent progressive signs of atherosclerosis and NASH, suggesting LHM to be a strong model for understanding the genesis of cardiometabolic diseases and developing new therapeutic strategies.

P269 / #1063, E-POSTERS TOPIC: 2. LIPIDS AND LIPOPROTEINS / 2.11 LIVER METABOLISM AND STEATOSIS

HEPATIC TRANSCRIPTIONAL EFFECTS OF SIMVASTATIN AND THE POSSIBLE IMPACT ON COVID-19

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Background and Aims: Recent reports show an association between statins therapy and reduction in 28-day all-cause mortality among Coronavirus disease 2019 (COVID-19) patients. This association is poorly understood mechanistically. Hence, we investigated whether simvastatin regulates hepatic expression of genes involved in humoral and innate immune responses, and in the activation of classical pathways of the complement system.

Methods: Forty patients eligible for cholecystectomy were randomized to 28-day treatments with simvastatin (80 mg/day), ezetimibe (10 mg/day), combination therapy (simvastatin + ezetimibe), or placebo before surgery. Liver biopsies were collected during the surgical intervention. Pooled RNA libraries were sequenced and RNA-seq reads were mapped to the human genome.

Results: A total of 260 genes were differentially expressed by the different treatment regimens. Of particular interest in the statin monotherapy is the downregulation of chemokine ligand 13 (CCL13), a novel marker of systemic immune activation during acute RNA viral infection. The gene
Background and Aims: The aim of this study was to assess the relationship between serum lipids and apolipoproteins and selected non-invasive parameters of kidney function in patients with type 2 diabetes mellitus (DM2) and NAFLD.

Methods: We examined 116 patients with DM2 from outpatient clinic. Serum apoA1, B100, B48 and C3, cystatin-C and uromodulin in urine were determined using ELISA method. Urinary albumin/creatinine ratio (ACR) was performed by standard methods.

Results: Mean age of patients was 59.1(11) years, mean value of HbA1c 8.6(2.3)%, and median (IR) creatinine 76(22) umol/l. Concentration of cystatin-C in urine (median, (IR)) was 9.78(17.10) ng/ml, and of uromodulin 8,6(2.3)%, and median (IR) creatinine 76(22) umol/l. Concentration of apoB48 and apoB100 were determined using ELISA method. Urinary albumin/creatinine ratio (ACR) was performed by standard methods.

Conclusions: Our pivotal study identifies immunomodulatory effects of a statin that contributes to the understanding of the recently proposed role of statin use in the novel coronavirus (SARS-CoV-2) infection and COVID-19 morbidity and mortality disease outcomes.

Background and Aims: Adipose tissue exposed to high fat diet affects extracellular matrix genes in the mesenchymal stem cell population.

Methods: We performed scRNA-seq in adipose tissue of control mice and atherosclerotic LDLR−/− / ApoB100/100 subjected to 1 (early disease) or 3 months (advanced disease) of HFD.

Results: This allowed us to identify 13 different cell types in the adipose tissue of the diseased mice. Among them, we identified mesenchymal cells (MSC) undergoing changes from putatively adipogenic to fibrogenic cells. The differentially expressed genes in the MSC population exhibited functions related to ECM development, maintenance and signaling. We also plan to perform scRNA-seq on the adipose tissue of ApoE−/− Fbn1−/−/Smad3−/− mice on HFD as Fibrillin-1 was one the genes of potential interest upregulated in the MSC population.

Conclusions: Altogether, our analysis provides the first steps toward understanding the role of MSCs in ECM-related changes during atherosclerosis and HFD stimulation.

Background and Aims: Introduction: Adipokines, expressed by adipose tissue, have been associated with metabolic disturbances and coronary artery disease. Adiponectin has anti-atherogenic and anti-diabetic properties, by inhibiting tumor necrosis factor (TNF-α). Elevated levels of visfatin and TNF-α are associated with atherosclerosis. Aim: Investigate effects of long-term exercise on circulating levels and adipose tissue expression of adiponectin, visfatin and TNF-α, and explore associations between adiponectin and physical performance, assessed by VO2peak, and glucometabolic variables.

Methods: Patients with type-2 diabetes and coronary artery disease (n = 137), 41-81 years, 17.2% females, were randomized in a 1:1 fashion to exercise and control groups. The exercise group underwent 1 year of 150 min weekly combined strength and endurance exercise. Blood and AT samples were obtained at baseline and after 12-months. Serum protein levels were measured by ELISA. RNA was extracted from adipose tissue and expression levels were relatively quantified by PCR.

Results: After intervention, there were no differences in changes between groups in circulating levels and AT-expression of the investigated markers. Changes in circulating adiponectin and VO2peak correlated significantly after 1 year (r = 0.256, p = 0.008), observed to be stronger in subjects with body mass index below median level (c<29 kg/m²) (r = 0.365, p = 0.007), still significant after adjusting for age, sex and advanced vascular disease (p = 0.046).

Conclusions: In patients with concomitant diabetes and coronary artery disease, exercise training seems to have limited impact on adipose tissue expression. Increased serum adiponectin levels were associated with improved VO2peak, especially in leaner subjects.