reduced in overweight NASH (p = 0.018). Lean NASH appeared similar to controls in microbiome alpha diversity and different from overweight and obese NASH (p = 0.05). A fibrosis score higher or equal than 2 was associated with increased abundance of Lactobacilli (p = 0.0007). Lean NASH had a higher caloric and lipid intake than overweight and obese NASH, however this was not associated with a specific gut microbiome composition.
Conclusions: Our data show that lean NASH patients have a specific microbiome composition compared to their overweight/obese counterparts and healthy subjects. A fibrosis score higher or equal than 2 but no single macronutrients intake was associated with fecal gut microbiome composition.

THU-381
Influence of UCP3 gene polymorphisms on metabolic syndrome and cardiovascular risk in patients with in non-alcoholic fatty liver disease
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Background and Aims: The uncoupling protein 3 (UCP3) gene region has been associated with energy metabolism and metabolic traits, as body mass index (BMI) changes and diabetes. The authors aimed to evaluate the possible association between UCP3 gene polymorphisms with non-alcoholic fatty liver disease (NAFLD), metabolic syndrome (MS), and cardiovascular disease (CVD) risk.
Methods: A population of 239 patients with NAFLD was recruited in a cross sectional study. Of these, 161 patients already had liver biopsy and were tested for three non-synonymous single nucleotide polymorphisms (SNPs) in the UCP3 gene rs11235972, rs3781907 and rs1726745 by the TaqMan method. Anthropometric, clinical and laboratorial data were registered. Odds ratios (OR) with its 95% confidence intervals (CI) were computed for the minor allele of each SNP in a codominant or recessive model. Correction for multiple comparisons due to multiple SNP testing took into account the effective number of independent tests based on the degree of linkage disequilibrium between SNPs. A value of $p \leq 0.02$ was considered as significant for genotype-related comparisons.
Results: NASH patients (n = 135) had the mean age of 56 ± 9.3, 54%, was female and MS was present in 84.9%. Besides, NASH patients had higher BMI (p = 0.01) and insulin levels (p = 0.02), as well as a higher frequency of diabetes (p = 0.03) than NAFL patients. The T allele of rs1726745 showed association with lower occurrence of MS (OR = 0.25, 95% CI: 0.08–0.75, p = 0.01) and lower values of aspartate amino transferase (AST) (CC = 50.18 ± 4.96 vs. XT = 31.14 ± 3.48, p = 0.0008), alanine amino transferase (ALT) (CC = 72.98 ± 7.29 vs XT = 44.43 ± 6.48, p < 0.0001) and triglycerides (TG) (CC = 214.12 ± 16.99 vs. XT = 160.24 ± 12.05, p = 0.01). In in the other hand, the rs3781907 and rs1125972 polymorphisms were associated with lower values of gamma glutamyl transferase (GGT) (AA = 90.67 ± 9.00 vs. XG = 56.98 ± 11.00, p = 0.003 and GG = 85.47 ± 8.30 vs. XA = 56.54 ± 13.41, p = 0.005, respectively), although, no association was found with the presence or absence of MS. No association was found between genotype frequencies of UCP3 polymorphisms to predict NAFL or NASH in liver biopsy.
Conclusions: The rs1726745 UCP3 gene polymorphism was associated with lower occurrence of MS and lower values of AST, ALT and TG. The rs3781907 and rs11235972 UCP3 gene polymorphisms may not be important determinants of MS in NAFLD patients, but showed association with lower values of GGT. These factors may contribute to reducing CVD risk in this population.

THU-382
Anti-steatotic effects in conjunction with lowering of PNPLA3 mRNA exerted by LXR inverse agonists in human hepatocytes and in rodent models of non-alcoholic fatty liver disease
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Background and Aims: Activation of Liver X Receptor (LXR) in the liver by potent, synthetic agonists is known to result in severe steatosis and hypertriglyceridemia in various animal models but an effective treatment of non-alcoholic fatty liver disease (NAFLD) requires the opposite. Thus, we have designed and synthesized LXR inverse agonists with the aim to inhibit LXRs pro-steatotic transcriptional activity. These compounds were used to demonstrate the effects on LXR inhibition in human hepatocytes and in mouse and rat models of NAFLD.
Methods: Compounds PX-L493 and PX-L603 were characterized in cellular reporter assays as inverse agonists of LXRalpha and beta [EC_{50} for LXR(α/β) in NCoR recruitment cellular assay = PX-L493 (5.3/1.4 nM); PX-L603 (966/326 nM)]. In human primary hepatocytes addition of LXR inverse agonists dose-dependently reduced the hepatocyte lipid load. Furthermore, the PX compounds demonstrated an inhibition of *de novo* lipogenesis in this cellular model as evidenced by [1,2-^{13}C]-acetate incorporation and mass isotopomer distribution analysis (MIDA). For an *in vivo* NAFLD model, Zucker (fa/fa) rats or C57 mice, were maintained on a high fat diet with 1% cholesterol for two weeks. Thereafter, they were either administered the PX-L603 or PX-L493 at 10 mg/kg or vehicle for another 2 weeks (rats) or 4 weeks (mice) on the same diet.
Results: Analysis of the hepatic lipid content yielded a significant reduction of triglycerides and cholesterol in animals treated with PX-L603 or PX-L493 compared to vehicle treatment. Gene expression analysis of candidate genes in the liver by qRT-PCR showed that the LXR compounds repressed known LXR target genes involved in fatty acid synthesis, uptake, triglyceride storage or export such as *Scd-1*, *Fas*, *Angptl-4*, *Cd36*. Of special note, treatment of C57 mice with PX-L603 yielded a potent reduction of *Pnpla3* mRNA, a gene that is associated with human NASH. MCP-1 mRNA expression in liver is significantly reduced pointing at anti-inflammatory effects in this model.
Conclusions: We have demonstrated that reducing LXRs transcriptional activity in human hepatocytes or in the liver of Zucker (fa/fa) rats or C57 mice by synthetic inverse agonists yields clear anti-steatotic effects through multiple mechanisms such as prevention of intestinal lipid uptake and inhibition of *de novo* lipogenesis. This suggests that inhibition of the LXR pathway in the liver is a useful novel approach for a pharmacotherapy of NAFLD.

THU-383
High fat diet related liver damage anticipates the appearance of cardiac injury: the role of Klf15 and tafazzin
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Background and Aims: The real impact of High Fat Diet (HFD) on the occurrence of Non-alcoholic Fatty Liver Disease NAFLD) and cardiovascular damage is still not well defined. As well, the timing and the molecular bases that link the onset of hepatic steatosis and its progression toward the appearance of the cardiovascular damage are not clear. The purpose of this study was to evaluate, in HFD fed mice (a known model of steatosis) and in NAFLD patients, the correlation between the modulation of some adipogenic genes expression and the damage occurring in liver and heart.

Methods: A panel of 84 adipogenic genes was analyzed in liver and heart of mice fed with HFD for 3, 6 and 12 months, in biopsies and in peripheral blood mononuclear cells (PBMC) from NAFLD patients with or without hypertension.
Results: We highlighted a different timing in gene expression profiling between liver and heart. In particular, the modulation observed in livers from 3 months HFD-fed mice was appreciable in the hearts only later. Gene expression profile from PBMCs of NAFLD patients faithfully reflected what observed in biopsies and was similar to that observed in 3 months HFD mice livers. Interestingly, we observed a particular time modulation in liver and heart of Krüppel-like factor 15 (Klf15) and Tafazzin genes and their protein levels.
Conclusions: We experience the existence of a liver-heart axis, indicating liver as the "primum movens" in inducing cardiovascular damage related to HFD intake. The adipogenic gene expression changes, in the heart, reflect those previously occurred in the liver of HFD mice. We highlight Klf15 and Tafazzin genes as possible novel biomarkers of liver damage progression as well as warning biomarkers for the initial onset of cardiovascular damage. Furthermore, we highlight that PBMCs might give the chance to be used as a non invasive tool to follow the progression and the consequences of high fat diet intake.

THU-384
Role of the intestinal vitamin D receptor in obesity, adipose tissue inflammation and hepatic lipid accumulation

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Background and Aims: Hypovitaminosis D is frequently observed in the obese population and in patients with non-alcoholic fatty liver disease (NAFLD), resulting in suggestions for vitamin D supplementation as a potential therapeutic option. Most physiological effects of vitamin D are mediated via the nuclear vitamin D receptor (VDR). However, the pathomechanistic contribution of the vitamin D- VDR axis to obesity and associated metabolic disorders is largely unknown.
Methods: We analyzed the pathophysiological role of global and intestinal VDR signaling in diet-induced obesity (DIO) using global *Vdr*−/− mice and mice re-expressing an intestine-specific human VDR transgene in the *Vdr* deficient background (*Vdr*−/− hTg). Phenotyping was performed by histological examination of liver and adipose tissue, gene expression analysis, measurement of serum/fecal parameters and the analysis of lipoprotein lipase (LPL) activity in adipose tissue.
Results: *Vdr*−/− mice were protected from DIO, hepatosteatosis and metabolic inflammation in adipose tissue and liver in comparison to control mice (*Vdr*+/−). Interestingly, this protection was less pronounced in *Vdr*−/− hTg animals which showed increased weight gain, adipose tissue inflammation and hepatic steatosis compared to *Vdr*−/− animals. In the intestine, VDR-dependent differential regulation of genes involved in lipid metabolism could be detected. These changes included an increased expression of the LPL-regulatory factor angiopoietin-like 4 (*Angptl4*) in *Vdr*−/− mice. In line with these differences in gene expression, VDR-dependent changes in adipose tissue LPL activity and serum triglyceride levels were observable among the different genotypes.
Conclusions: In conclusion, our study suggests the existence of a VDR-mediated metabolic cross-talk between gut and adipose tissue, which significantly contributes to systemic lipid homeostasis and the development of obesity and associated metabolic inflammation. As a mechanistic explanation, our data suggest a VDR-dependent regulation of intestinal Angptl4 which, in turn, controls the uptake of circulating lipids into peripheral organs such as adipose tissue. This implicates a potential role of the intestinal VDR as a drug target for the modulation of lipid metabolism in obesity and metabolic disorders.

THU-385
NorUDCA improves liver injury and metabolic situation in mouse models of obesity and steatosis

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Background and Aims: Bile acids have signaling functions and regulate a variety of metabolic and inflammatory pathways. Ursodeoxycholic acid (UDCA) is used as therapeutic drug in humans, but showed only limited efficacy in NASH. NorUDCA is a side-chained shortened UDCA derivative and improves liver damage in mouse models of cholestasis, bile duct or parasitic injury. We aimed to explore whether NorUDCA improves steatosis and other features of metabolic syndrome in mouse models.
Methods: Ob/ob mice were fed 0.5% NorUDCA (ob/ob treatment n = 7) or chow (n = 7) diet for 6 weeks. WT mice received high-fat-diet for 29 weeks (HFD n = 7), HFD with 0.5% NorUDCA (prevention n = 6), or HFD for 22 weeks following 7 weeks of HFD with 0.5% NorUDCA (rescue n = 6). Metabolic characterizations were achieved by metabolic cages, IPGTT and IPITT. Food, water intake and bodyweight were recorded weekly. Serum biochemistry, liver histology, hepatic and adipose tissue mRNA and protein expression of inflammatory, ER-stress, lipid and glucose metabolism genes were analyzed. Fatty acid profiling was performed from stool. Microbiome was analyzed by 16s sequencing from cage and individual feces samples from two different mouse houses.
Results: NorUDCA treatment reduced liver enzymes (ALT, AST, AP) in prevention (−30%), rescue (−65%) and ob/ob treatment settings (−60%). Prevention and rescue with NorUDCA under HFD reduced bodyweight, whereas ob/ob treatment did not. Steatosis and HOMA-IR were clearly reduced in prevention and rescue settings. Prevention and ob/ob treatment with NorUDCA resulted in faster glucose clearance. Prevention and rescue with NorUDCA under HFD interfered with intestinal fat absorption as reflected by increased free fatty acids (>16 mg/g faeces). Prevention, rescue and ob/ob treatment with NorUDCA improved hepatic inflammation as reflected by lower Mcp1 (−64%) and Tnfα (−43%) in liver. In adipose tissue F4/80 expression was reduced in prevention (−93%) and obob treatment (−35%). NorUDCA treatment reduced Firmicutes and increased Bacteroidetes abundance. Bray-Curtis plot showed similar effects of NorUDCA treatment on microbiome in two different mouse houses and in HFD and ob/ob mouse model.
Conclusions: NorUDCA reduced liver injury in a genetic and a dietary fatty liver mouse model. Furthermore the inflammation and overall metabolic improvement corresponded with changes in intestinal microbiota. Therefore NorUDCA may be a new pharmacological treatment option in fatty liver disease and clinical studies are warranted.