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Abstract Issue

P0014 GUT MICROBIOTA SIGNATURES IN TURKISH NAFLD PATIENTS.

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Introduction: The bacterial overgrowth in the intestine, disruption of the balance in the gut microbiota (dysbiosis) may have an effect on NAFLD pathogenesis. The purpose of the present study is to compare the gut microbiota of the patients with NAFLD and the healthy controls by quantitative Real Time PCR (qPCR) analysis. Gut microbiota is affected by environmental and specific dietary patterns. This is the first study in Turkish NAFLD patients with diverse cultural dietetic habits. In order to understand the potential role of gut dysbiosis and subsequent translocation of bacterial products, serum endotoxin levels were also analyzed.
Aims & Methods: The stool and serum samples from 52 NAFLD patients and 38 healthy controls have been collected. qPCR analysis of *Akkermansia muciniphila*, *Faecalibacterium prausnitzii*, *Lactobacillus spp*., *Bifidobacterium spp*., *Bacteroides fragilis* group was performed. Serum endotoxin levels were also determined by Chromogenic LAL Assay. Dietary habits were analysed by nutritional questionnairs.
Results: *Akkermansia muciniphila* and *Bacteroides fragilis* group were significantly lower in patients with NAFLD as compared with the healthy control ($p < 0.001$). No significant difference was determined in terms of *Lactobacillus spp*., *Bifidobacterium spp*. and *Faecalibacterium prausnitzii* counts. Moreover, significantly elevated endotoxin levels were determined in NAFLD patients (9.04 EU/mL in NAFLD group; 2.75 EU/mL in control group; $p < 0.05$).
Conclusion: *Akkermansia muciniphila* and *Bacteroides fragilis* group has been known to have beneficial effects on gut barrier function. These two bacterial groups were decreased in Turkish NAFLD patients. Decreased levels of these bacteria were also shown in metabolic syndrome, which is frequently associated with NAFLD. NAFLD patients have also increased endotoxin levels which indicate a translocation of bacterial products as a result of increased gut permeability.
Disclosure of Interest: All authors have declared no conflicts of interest.

P0015 RETROSPECTIVE ANALYSIS OF THE MICROBIAL EPIDEMIOLOGY OF SPONTANEOUS BACTERIAL PERITONITIS AND BACTERIASCITES IN PATIENTS WITH LIVER CIRRHOSIS

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Introduction: Current guidelindes recommend the use of 3rd generation cephalosporines for antibiotic therapy of spontaneous bacterial peritonitis (SBP). Response rates to this therapy are reported with 76–98%. Bacterial translocation of grampositive bacteria including enterococcae and specific local resistance patterns may result in inferior response rates to 3rd generation cephalosporines. Knowledge on local microbial epidemiology privides evidence to optimize antibiotic therapy.
Aims & Methods: Microbial epidemiology of ascitic fluid cultures and resistance patterns obtained from patients with liver cirrhosis between 2013–2015 at a tertiary care center (Krankenanstalt Rudolfstifung, Vienna) were retrospectively analyzed.
Results: In total 482 ascites cultures of 200 cirrhotic patients were analyzed. Median age was 62.2 (31.2–91.8) years, the majority (73%, M:146/F:54) were men, and the main etiology was alcoholic liver disease (83% ALD), followed by viral hepatitis (8.9%), autoimmunie (0.8%), and cryptogenic (7.3%). Thirty-one (6.4%) of ascitic fluid cultures reveiled positive results, and 12.5% of all patients (25/200) had at least one positive culture result. While 17 (3.5%) of patients had bacteriascites, 58 (12%) of patients had SBP – among those 47 (81%) had no germ isolated at their asicitic fluid culture. The most common species were *Streptococcus spp*. (n = 7/22.6%) followed by *Candida spp*. (n = 6/19.4%), *E. coli* and *Staphylococci* (n = 5/16.1%) and *Enterococci* (n = 3/9.7%). 28% of all bacteria were resistant towards aminopenicillines/betalactamase-inhibitors. There was a resistance rate of 18.5% of all germs towards 3rd generation cephalosporines.
Conclusion: Considering the local microbial epidemiology, the initial empirical antibiotic treatment for SBP should have good efficacy from grampositive bacteria including Enterococci. The recommendation for empiric antibiotic therapy of patients with liver cirrhosis with inherent immunosuppression should be adapted according to local resistance rates.
Disclosure of Interest: All authors have declared no conflicts of interest.

P0016 THE ADAPTOR PROTEINS CARDIF/STING NEGATIVELY REGULATE THE PROLIFERATION OF LIVER REGENERATION AFTER PARTIAL HEPATECTOMY IN MICE

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Introduction: The innate immune system is of crucial importance for the regulation of liver regeneration. Nucleic acid sensors are know to play a major role within this context, however, there is only limited knowledge on the role of central adaptor proteins, such as CARDIF and STING, during liver regeneration. The aim of the present study was to analyze CARDIF and STING during liver regeneration. Our hypothesis states that these known modulators of the innate immune system have an influence on liver regeneration by direct activation of CARDIF/STING-dependent cytosolic sensors.
Aims & Methods: In order to examine the influence of these two proteins on liver regeneration, we use a newly established CARDIF/STING knockout mouse model and compared it to a C57BL/6 mice control cohort. A 2/3 partial hepatectomy (PH) was performed in both groups and mice were analyzed at eight designated timepoints after surgery (n = 80 mice in total). Liver regeneration was quantified by liver-to-body weight ratio, while proliferation was determined by BrdU staining. Additionally, RNA- and protein levels of proliferation markers were analyzed in resected tissues while pro-inflammatory cytokines were measured in murine serum.
Results: CARDIF/STING knockout mice showed a significantly impaired liver regeneration after PH. Additionally, we detected a strong difference in BrdU staining at several time points after PH underlining an inhibition of proliferation in the absence of CARDIF and STING. Expression analysis of Interleukin-6 (IL-6) revealed a significant decrease in the wild type cohort after PH. In addition, the membrane-bound form of the IL-6 receptor was found to be increased in the control group 2, 4 and 8 h after PH, while the soluble form of the receptor was significantly increased 12 h post-PH. In CARDIF/STING knockout mice, the proliferation marker Cyclin D1 was decreased until 24 hours after surgery, while $p21^{Cip1}$ expression, which is associated with a cell cycle arrest, was increased 8 h post-PH.
Conclusion: Together, these data provide the first experimental evidence that CARDIF/STING knockout mice show a delayed liver regeneration. These data support the concept that CARDIF and STING play a major role in liver regeneration during physiological conditions. In the absence of these two proteins, we observed a modulated immune response which lead to a negative regulation of the proliferative capacity in liver after partial hepatectomy. This finding could impact on the future development of molecular therapies making use of the innate immune system.
Disclosure of Interest: All authors have declared no conflicts of interest.

P0017 THE ROLE OF GENETICALLY MODIFIED HSCS IN LIVER REGENERATION AFTER ACUTE LIVER DAMAGE

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Introduction: Actual problem of modern hepatology is to find a new treatment for liver diseases. Nowadays gene and cell therapy methods using hepatic stellate cells (HSCs) that are thought to be regional stem cells of the liver, are considered as a new perspective approach. It is assumed that using genetically modified cells that express and overexpress therapeutic factors, could reduce the therapeutic dose of transplanted cells and enhance therapeutic effects of these cells. However, it remains unclear, the influence of genetically modified cells, in this case HSCs, on liver regeneration and therapeutic effects of these cells after transplantation into the organism.
Aims & Methods: We aimed to study the role of genetically modified HSCs (by using the adenoviral vector Ad5-optHGF-optFGF4-RFP) on liver regeneration after transplantation into the rats with acute liver damage. Genetic modification of HSC was carried out by using adenoviral vector Ad5-optHGF-optFGF4-RFP, which contains hepatocyte growth factor (HGF), fibroblast growth factor-4 (FGF-4), and red fluorescent protein (RFP). We selected the classical model of acute liver damage – partial hepatectomy (PH). Genetically modified HSC were injected into portal vein during the PH operation. Control group of animals have received the same cells without PH operation. The animals were sacrificed after 1, 2, 3, 5, 7, 14, 28 days after the transplantation of HSC. Paraffin slices were stained by immunohistochemistry with antibodies to RFP, desmin – marker of HSC and a-SMA – myofibroblast marker.
Results: RFP + cells were detected in parenchyma in both groups even at first days after transplantation. They varied in shape and location in the liver in different days of experiment. Small oval-shaped RFP + cells were stained from the first day near the portal tracts. At the same time hepatocyte-like RFP + cells were also found here from the first day. Maximal number of such cells was found on the 5th day after transplantation in both groups, but in the experimental group average number of cells was higher than in control. Coincidently, the intensity

and quickness of hepatocyte repopulation in liver were higher in the group of animal after PH. Number of desmin + cells increased more in the experimental group comparing with the control one. In both groups a-SMA-positive cells were not detected.
Conclusion: Genetically modified HSCs, which is transduced by HGF and FGF-4 genes, save their viability after transplantation into the rat after PH, migrate and integrate into the liver parenchyma. These cells have a positive influence on the process of liver regeneration without the risk of liver fibrosis.
Disclosure of Interest: All authors have declared no conflicts of interest.

P0018 ANGIOTENSIN II TYPE 1 RECEPTOR GENE A1166C POLYMORPHISM IS ASSOCIATED WIT NON ALCOHOLIC FATTY LIVER DISEASE AND PREDICTS ITS SEVERITY

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Introduction: The pathogenesis of non alcoholic fatty liver disease (NAFLD) has not been well demonstrated yet, however, genetic predisposition is probably of major importance. Angiotensin II type I receptor (AGTR1) have been known to be involved in the process of liver fibrosis and metabolic syndrome.
Aims & Methods: This study aimed to investigate the association between AGTR1 A1166C polymorphism and NAFLD. A cross-sectional study was conducted between March 2014 and March 2015 among healthy adult individuals referred to our radiology clinic for abdominal ultrasonography. NAFLD was diagnosed by an expert radiologist based on the presence of these ultrasonographic findings: hepatorenal echo contrast, liver brightness, deep attenuation, vascular blurring and the absence of hepatitis B surface antigen or antibody to hepatitis C virus, 2) alcohol consumption (>20 g/day), 3) history of other causes of liver disease, and 4) medications known to produce fatty liver disease during the last six months prior to the study. Participants' characteristics and their lab data including liver function tests, lipid profile, fasting plasma glucose (FPG) were also recorded. AGTR1 A1166C polymorphism was checked in subjects with NAFLD and healthy controls using TaqMan allelic discrimination method.
Results: Fifty eight subjects with NAFLD were compared with 88 individuals without NAFLD. Mean of all anthropometric indices including BMI, weight, height, waist circumference and hip circumference were significantly higher in subjects with NAFLD compared to those without NAFLD ($P < 0.05$). Mean total cholesterol was significantly higher in subjects with NAFLD in comparison to the controls in univariate analysis ($P = 0.018$). Higher serum ALT was also a predictor of NAFLD (38.56 ± 17.61 versus20.76 ± 6.40 IU/L) ($P = 0.0001$). Metabolic syndrome was detected in 31 (53.44%) individuals in NAFLD group and in 27 (19.01%) in control group ($P < 0.001$) (OR: 3.51, 95% CI: 1.84–6.66). Multivariate logistic regression analysis of risk factors showed that body mass index (BMI), metabolic syndrome, waist circumference, hip circumference and serum ALT were independent predictors of NAFLD in our study population. The frequency of AA and CC genotypes of AGTR1 gene was significantly higher in patients with NAFLD compared to controls ($P = 0.029$ and $P = 0.042$ respectively). Furthermore, C allele was more detected in subjects with NAFLD compared to healthy controls (OR: 2.1; 95% CI: 1.23–3.61, P-Value = 0.006). CC genotype (OR: 10.62; 95 %CI: 1.05–106.57, P-Value: 0.045) and C allele (OR: 6.81; 95 %CI: 1.42- 32.48, P-Value: 0.016) were also predictors of severe fatty liver disease in our study population.
Conclusion: Our results provide the first evidence that AGTR1 gene A1166C polymorphism not only is associated with NAFLD and but also may predict its severity. Multivariate regression analysis for the NAFLD predictors.

	OR	(95% CI)	P-value
Body mass index (BMI)	7.74	(1.25-3.73)	0.005
Waist circumference	9.26	(0.68–0.92)	0.002
Hip circumference	5.21	(1.02–1.39)	0.022
Metabolic syndrome	15.21	(9.74–14.43)	<0.001
Alanine aminotransferase (ALT)	26.46	(1.19–1.50)	<0.001

Disclosure of Interest: All authors have declared no conflicts of interest.

P0019 PATIENTS WITH POLYCYSTIC LIVERS MORE THAN TWO TIMES THE NORMAL SIZE ARE LIKELY TO DEVELOP SYMPTOMS

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Introduction: Progressive growth of hepatic cysts can lead to symptomatic hepatomegaly in polycystic liver disease (PLD).
Aims & Methods: Our primary aim was to determine at which threshold of liver volume PLD patients become symptomatic. As a secondary objective we investigated which symptoms are associated with higher liver volume. We used the PLD questionnaire (PLD-Q), a validated questionnaire that assesses frequency and discomfort of PLD-related symptoms, to determine the symptom burden. In a cohort of 291 PLD patients that have completed the PLD-Q and rated themselves as symptomatic or not (NCT02173080), we have defined the PLD-Q cut-off value of being symptomatic with receiver operating characteristic (ROC) analysis. The optimal PLD-Q cut-off score was 31 points with an area under the curve (AUC) of 0.832 ($p < 0.001$). Next, we used baseline data of PLD patients from two prospective studies (DIPAK observational study and CURSOR randomized controlled trial (NCT02021110). All patients completed the PLD-Q and had liver volume imaging (CT or MRI) measured by segmentation. In order to determine the liver volume cut-off value for being symptomatic, we used the PLD-Q cut-off value from the previous step in another ROC analysis with liver volume as independent variable. Spearman correlations were calculated between symptoms and liver volume.
Results: We included 82 of the 131 patients from the prospective studies (main exclusions: no PLD n = 26, no PLD-Q n = 7 or no imaging n = 8). Most patients were female (n = 67) with a mean age of 48 years. Median liver volume was 3879 mL (IQR: 2452 – 5891). Cut-off liver volume for being symptomatic was 3472 mL (AUC 0.805, $p < 0.001$) with a sensitivity of 80% and a specificity of 73%. This cut-off volume has a positive and negative predictive value of 66% and 82% respectively. Dissatisfaction with abdomen size was strongly correlated with liver volume (r = 0.63). Fullness, early satiety, pain in rib cage, shortness of breath, limited mobility, anxiety about the future and, problems with intercourse correlated moderately (r = 0.40–0.59). There was a weak correlation with lack of appetite, pain in side and tiredness (r = 0.20–0.39). Nausea (r = 0.17, p = 0.146) and abdominal pain (r = 0.17, p = 0.127) were not correlated with liver volume.
Conclusion: Patients with liver volumes equivalent to two times the normal size are likely to develop PLD-related symptoms. In patients with smaller livers, other causes that lead to similar symptoms should be considered. Most PLD-related symptoms are associated with larger liver volume, except for nausea and abdominal pain.
Disclosure of Interest: All authors have declared no conflicts of interest.

P0020 LNCRNA PROFILE IN NAFLD AND IDENTIFICATION OF A PROTECTIVE NOVAL LNCRNA FLRL2 IN NAFLD

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Introduction: Non-alcoholic fatty liver disease (NAFLD) is one of the most prevalent chronic liver diseases worldwide with unclear mechanism. Long noncoding RNAs (lncRNAs) have recently emerged as important regulatory molecules in liver diseases.
Aims & Methods: To further understand the pathogenesis of NAFLD, lncRNA and mRNA microarray was conducted in NAFLD mice model. Potential target genes of significantly changed lncRNA were predicted using cis/trans-regulatory algorithms, followed by Gene Ontology analysis and KEGG pathway enrichment analysis. NAFLD mice model and NAFLD AML12 cell model were used in further experiments. Real-time qPCR and Western Blot were adopted in effect test after manipulations with certain siRNA or shRNA transfection. Oil Red O/ HE staining and total triglyceroil kit were applicated in celllular steatosis evaluation. Dual luciferase assay was used in identifying promoter activity of certain genes.
Results: In current analysis, 89 up-regulated and 177 down-regulated mRNAs were identified, together with 291 dysregulated lncRNAs. Bioinformatic analysis of these RNAs has categorized these RNAs into pathways including arachidonic acid metabolism, circadian rhythm, linoleic acid metabolism, Peroxisome Proliferator Activated Receptor signaling pathway, sphingolipid metabolism, steroid biosynthesis, tryptophan metabolism and tyrosine metabolism were compromised. Quantative PCR of 9 mRNAs and 8 lncRNAs of interest (named as fatty liver related lncRNA, FLRL) was conducted and verified previous microarray results. Several lncRNAs, such as FLRL1, FLRL6 and FLRL2 demonstrated to be likely a key player in circadian rhythm targeting Per3, Per2 and Arntl. While FLRL8, FLRL3 and FLRL7 showed their potential role in PPAR signaling pathway through interaction with Fabp5, Lpl and Fads2. Mechanism of FLRL2 as well as its potential target circadian rhythm gene Arntl was investigated. Western blot and qPCR both revealed a decreased trend of FLRL2 as well as Arntl in NAFLD in vivo, in vitro models. Overexpression of FLRL2 reverses lipid accumulation, ER stress and lipogenesis, which are main