

## POSTER PRESENTATIONS

### THU-451

#### Effect of exercise on gut microbiota and metabolic status modulation in an *in vivo* model of early obesity and NAFLD

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**Background and Aims:** Childhood obesity is one of the most serious public health concerns from this century, associated with metabolic syndrome, nonalcoholic fatty liver disease (NAFLD) and gut microbiota alterations. Physical exercise improves obesity and NAFLD progression, modulating the gut microbial balance. We aim to investigate the effect of physical exercise on gut microbiota and the metabolic status of an *in vivo* model of early obesity, metabolic syndrome, and NAFLD.

**Method:** 21 days old male Wistar rats fed with control (C) or high fat diet (HFD) for 6 weeks followed a 5 weeks-interval aerobic training protocol. Body weight gain and metabolic markers were monitored. Lipid metabolism, pro-inflammatory and oxidative-related gene expression was assessed by RT-qPCR. The total bacteria concentration and the *Firmicutes/Bacteroidetes* ratio from faecal samples were assessed by qPCR.

**Results:** HFD increased body and adipose tissue weight gain (+14% and +44%, vs C, respectively), hepatic steatosis (NAFLD Index NAS:3.4), liver damage (AST:+12%; ALT:+45%, LDH:+36%, vs C), liver triglycerides (TG:+58%, vs C) and insulin resistance (HOMA-IR:+22%, vs C), impairing the gut-liver axis-related inflammation and leading to oxidative stress (TLR4:+286%; TNF $\alpha$ :+154%; NLRP3:+70%; CYP2E1:+380%, vs C). The increased intrahepatic lipid accumulation was associated with altered lipid metabolism-related gene expression (SREBP-1c:+94%; FAT/CD36:+95%; FAS:+57%, vs C). Exercise decreased body weight (-17%), insulin resistance (HOMA-IR:-37%), liver damage (ALT:-20%), NAS (-25%) and the intrahepatic lipid accumulation (-25%) as a result of its lipogenic metabolism modulatory capacity (SREBP-1c:-42%; FAT/CD36:-38%; FAS:-27%), reducing the subsequent lipotoxicity and the exercise ability to improve the inflammatory response induced by the gut-liver axis alteration (TLR4:-26%; TNF $\alpha$ :-5%; NLRP3:-3%; CYP2E1:-43%). HFD-fed rats showed lower intestinal bacteria concentration and higher *Firmicutes/Bacteroidetes* ratio, dysbiosis that was partially reverted by exercise.

**Conclusion:** We provide scientific evidences supporting the use of physical exercise protocols to modulate the intestinal microbiota in the management of childhood obesity and NAFLD development, via its anti-inflammatory, lipid metabolism modulatory and prebiotic capacities. Funded by LE063U16 (Junta de Castilla y León y Fondo Europeo de Desarrollo Regional (FEDER)) y GRS1428/A/16. CIBERehd is funded by Instituto de Salud Carlos III (Spain).

### THU-452

#### The paracrine effect of visceral adipose tissue obtained at bariatric surgery on primary human hepatic stellate cells grown in human 3D healthy liver scaffolds

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**Background and Aims:** Emerging data indicate that the progression from simple steatosis (NAFL) to non-alcoholic steatohepatitis (NASH) results from converging pathophysiological events originating in the liver, the adipose tissue, and the gastrointestinal tract. Adipose tissue

is recognized as an endocrine organ that secretes adipokines controlling systemic metabolism and energy homeostasis. We previously showed that adipose tissue macrophages are activated in NASH and secrete pro-inflammatory cytokines which play a detrimental role during NAFL/NASH development. In this study the paracrine effect of human visceral adipose tissue (VAT) on primary human hepatic stellate cells (hHSC) cultured on 3D human liver scaffolds was explored.

**Method:** Freshly obtained VAT biopsies derived from obese patients and control patients undergoing bariatric surgery and cholecystectomy, respectively, were used for short-term culture (LEAN, NAFL and NASH patients). Similar-sized VAT explants were cultured in serum-free medium and conditioned medium was collected after 48 hrs. Human liver 3D scaffolds were obtained by the decellularization of healthy human liver unsuitable for transplantation. Primary hHSC were seeded for 7 days on 3D scaffolds and exposed to adipose tissue conditioned media (AT-CM) for 2x24 hrs. H&E staining was performed; RNA was extracted, followed by qPCR for pro-fibrogenic and pro-inflammatory genes.

**Results:** Primary hHSC homogeneously engrafted in the 3D scaffolds. No significant differences in the expression of pro-fibrogenic and pro-inflammatory genes was found in hHSC exposed to AT-CM derived from LEAN, NAFL and NASH patients and they were similarly upregulated when compared to non-treated cells. Importantly, within the group of samples from NASH patients, the upregulation of ACTA2 and COL1A1 was significantly more evident in samples with evident liver fibrosis. On the other hand, AT-CM derived from diabetic patients induced a significantly higher increase in pro-fibrogenic gene expression in hHSC 3D culture when compared with samples derived from non-diabetic patients, irrespective of the stage of liver fibrosis. HSC-related adipokines expression and characterization of the adipose tissue secretome is ongoing to further explore the mechanism of action on hHSC.

**Conclusion:** AT-CM-derived from NAFL and NASH patients, marked by different stages of hepatic steatosis, showed a paracrine effect on hHSC. This is the first study exploring the relationship between VAT and hHSCs on human liver 3D scaffold.

### THU-453

#### Integrative analysis of NGS data highlight a genetic variant in ATG7 gene as a novel risk factor for nonalcoholic fatty liver disease progression

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**Background and Aims:** Nonalcoholic fatty liver disease (NAFLD) represents an emerging cause of cirrhosis and hepatocellular carcinoma (HCC). NAFLD has a strong genetic component and the identification of causal variants underlying disease development and