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Protective Effect of Quercetin Treatment on Gut Microbiota Imbalance in Obesity-Associated NAFLD in Patients and in HFD-FED Mice

D. Porras[1], *M.V. García-Mediavilla*[1,2], *E. Nistal*[1,3], *S. Martínez-Flórez*[1], *S. Pisonero-Vaquero*[1], *J. Crespo*[4], *F. Jorquera*[2,3], *J.L. Olcoz*[2,3], *R. Jover*[2,5], *J. González-Gallego*[1,2], *S. Sánchez-Campos*[1,2]

[1]Institute of Biomedicine IBIOMED, University of León, León, Spain; [2]Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas CIBERehd, Instituto de Salud Carlos III, Madrid, Spain; [3]Department of Gastroenterology, Complejo Asistencial Universitario de León, León, Spain; [4]Gastroenterology and Hepatology Department. Research Institute Marqués de Valdecilla IDIVAL, Marqués de Valdecilla University Hospital, Santander, Spain; [5]Experimental Hepatology Unit, IIS Hospital La Fe, Valencia, Spain

Background and Aims: Gut microbiota is involved in obesity, metabolic syndrome and nonalcoholic fatty liver disease (NAFLD). Quercetin may modulate the intestinal microbiota composition, suggesting therapeutic potential in NAFLD. The present study aims to establish the role of gut microbiota imbalance in obesity-related NAFLD development in patients and in an *in vivo* model and to investigate benefits of experimental treatment with quercetin.

Methods: Gut bacterial communities were identified by pyrosequencing of the 16S rRNA extracted from faecal samples of obese patients and from caecal samples of mice fed with high fat diet (HFD) with or without quercetin for 16 weeks. Hepatic TLR-4-NF-κB signaling pathway activation, inflammasome response, endoplasmic reticulum stress induction, as well as intestinal barrier dysfunction were analyzed.

Results: Pyrosequencing analysis of human faecal samples showed significant differences in the phylum *Proteobacteria* and *Firmicutes* between obese patients and controls. However, obese patients not showed a different *Firmicutes*/*Bacteroidetes* ratio compared with controls. Significant differences in the proportion of bacterial genera within gut microbiota of obesity-related NAFLD were shown in comparison to control group, supporting the role of dysbiosis in NAFLD development. In our murine model, metagenomic studies revealed differences at phylum, class and genus levels induced by HFD, leading to dysbiosis, characterized by an increase in *Firmicutes/Bacteroidetes* ratio and in Gram-negative bacteria and a lower concentration of the total bacteria. Quercetin blocked gut microbiota imbalance, showing prebiotic capacity. At genus level, we found an increase in *Helicobacter* genus, which was reverted by quercetin treatment. NAFLD severity correlated with dysbiosis markers, indicating a microbiota-dependent individual metabolic phenotype. HFD-induced dysbiosis was associated whith impaired intestinal SCFAs production and barrier integrity. HFD-related endotoxemia was accompanied by TLR-4-NF-κB pathway activation, inflammasome response and endoplasmic reticulum stress. Treatment with quercetin restored SCFAs production and intestinal barrier function, reducing the activation of NF-κB, and inhibiting overexpression of inflammatory components and reticulum stress markers.

Conclusions: Our data support the role of dysbiosis in NAFLD development, sustaining the suitability of quercetin as a therapeutic approach for obesity-associated NAFLD.

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Fatty Liver and Epidemiology

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Serum Vitamin D Correlates Inversely with Hepatic Vitamin D Receptor Levels in Non-Alcoholic Fatty Liver Disease Patients: Relationship with Histological Severity and Endocrine Co-Morbidities

C. Garcia-Monzon[1], *E. Del Pozo-Maroto*[1], *Á. González-Rodríguez*[1], *J. Rodríguez de Cía*[1], *A. Casado-Collado*[1], *J. Vargas-Castrillón*[1], *A. Saez*[1], *O. Lo Iacono*[2], *R. Jover*[3]

[1]Santa Cristina University Hospital, Liver Research Unit, Madrid, Spain; [2]Hospital del Tajo, Sección de Gastroenterologia, Aranjuez- Madrid, Spain; [3]Instituto de Investigación Sanitaria La fe, Experimental Hepatology Unit, Valencia, Spain

Background and Aims: In order to evaluate the impact of different endocrine disorders as risk factors, either alone or in combination, for non-alcoholic fatty liver disease (NAFLD) progression, we aimed to determine both serum vitamin D and hepatic vitamin D receptor levels as well as serum thyroid hormones and gonadotropin concentrations in NAFLD patients.

Methods: Serum vitamin 25-OH-D_3 (VD), thyroid-stimulating hormone, free thyroxin, follicle-stimulating hormone and luteinizing hormone concentrations along with hepatic vitamin D receptor mRNA levels were quantified by chemiluminescent immunoassays and real-time PCR, respectively, in 99 patients with biopsy-proven NAFLD: 19 non-alcoholic steatohepatitis (NASH), 80 non-alcoholic fatty liver (NAFL) and 89 subjects with histologically normal liver (NL).

Results: A high prevalence of VDD was found in our study population, but no significant differences were observed between NL subjects (64%) and NAFLD patients (70%). Since we had previously shown that hepatic VDR mRNA levels were significantly higher in NAFLD patients, largely in those with NAFL, than in NL subjects (Bozic et al, J Hepatol 2016), we wanted to explore the potential relationship between serum VD and hepatic VDR mRNA levels. Interestingly, serum VD concentrations correlated inversely with hepatic VDR mRNA levels only in patients with NAFL ($r = -0.570$, $p = 0.003$) but not in those with NASH ($r = 0.067$, $p = 0.865$). In contrast, a positive correlation was found between serum VD concentrations and hepatic VDR mRNA levels in NL subjects ($r = 0.570$, $p = 0.033$). Moreover, considering the entire study cohort, serum VD cor-