The gut-liver-muscle axis in liver cirrhosis: Does the gut microbiome dysbiosis contribute to sarcopenia?

Summary

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Supervisor:	Prof. Dr. Vanessa Stadlbauer-Köllner
Availability:	This position is available.
Offered by:	Medical University of Graz
Application deadline:	Applications are accepted between February 04, 2019 00:00 and March 31, 2019 23:59 (Europe/Zurich)

Description

Background:

Liver cirrhosis is a common health problem leading to more than 1 million deaths per year, many of them in young and middle-aged people. More than 50% of patients with liver cirrhosis suffer from sarcopenia, leading to complication including a higher mortality risk and a loss in quality of life and working capacity (1, 2). The mechanisms of sarcopenia in cirrhosis are poorly understood and therefore no specific therapeutic approaches are available. The composition of the gut microbiome is altered in liver cirrhosis and contributes to an increased gut permeability, intestinal bacterial translocation and inflammation (3-8). The gut microbiome may influence muscle metabolism via inflammatory or metabolic pathways (9).

Hypothesis:

We hypothesize that the composition and function of the faecal microbiome is altered in cirrhosis, leading to increased gut permeability, translocation of bacterial products and metabolites and inflammation, which contributes to the development of sarcopenia. Therefore, the aim of the study is to perform a clinical study to obtain biomaterial from patients with liver cirrhosis with and without sarcopenia in order to assess a large number of biomarkers, perform *in silico* data modelling and cell culture studies to understand the mechanistic interplay between gut microbiome and muscle metabolism.

Objectives of the study are:

1. To study diversity, taxonomic composition and function of the faecal microbiome in liver cirrhosis patients with and without sarcopenia
2. To study faecal, serum and urine metabolome composition as well as gut permeability, inflammation and bacterial translocation in these patients
3. To search for markers of dysbiosis, microbial metabolism, gut permeability, inflammation and bacterial translocation to identify the most likely factors influencing sarcopenia
4. To test the identified molecules in cell culture studies to discover potential diagnostic and therapeutic targets

Methodology:

All patients will be thoroughly assessed for sarcopenia, gut barrier function, bacterial translocation and inflammation with a broad range of clinical marker and biomarker. Furthermore, in this cohort, a multi-omics approach assessing the composition and function of the gut microbiome and the stool, serum and urine metabolom using 16s rRNA sequencing, shot gun sequencing and NMR metabolomics methods will be performed. This will be followed by *in silico* modelling using univariate regression methods, supervised learning analysis with Random Forest Algorithms, LDA effect size and Least absolute shrinkage and selection operator (LASSO) to identify biomarker signatures associated with sarcopenia. The results from this in silico approach will be used for mechanistic cell culture studies to assess the pathophysiological role of the identified microbial species and metabolites in the development of sarcopenia.

Expected Outcome:

The PhD student within this project will learn a large variety of clinical assessments, laboratory techniques and will develop thorough bioinformatics knowledge. The results of this project will help to better understand the pathophysiology of sarcopenia in liver cirrhosis and will allow the development of targeted therapeutic interventions. These results will directly impact of patient care and will hopefully enable us to prevent and treat sarcopenia in cirrhosis in order to improve survival and quality of life in these patients.

References:

1. Maharshi S, Sharma BC, Srivastava S. Malnutrition in cirrhosis increases morbidity and mortality. J Gastroenterol Hepatol. 2015;30(10):1507-13
2. Moctezuma-Velazquez C, Garcia-Juarez I, Soto-Solis R, Hernandez-Cortes J, Torre A. Nutritional assessment and treatment of patients with liver cirrhosis. Nutrition. 2013;29(11-12):1279-85
3. Bajaj JS, Heuman DM, Hylemon PB, Sanyal AJ, White MB, Monteith P, et al. Altered profile of human gut microbiome is associated with cirrhosis and its complications. Journal of hepatology. 2014;60(5):940-7
4. Bajaj JS, Ridlon JM, Hylemon PB, Thacker LR, Heuman DM, Smith S, et al. Linkage of gut microbiome with cognition in hepatic encephalopathy. American journal of physiology Gastrointestinal and liver physiology. 2012;302(1):G168-75
5. Qin N, Yang F, Li A, Prifti E, Chen Y, Shao L, et al. Alterations of the human gut microbiome in liver cirrhosis. Nature. 2014;513(7516):59-64
6. Schnabl B. Linking intestinal homeostasis and liver disease. Current opinion in gastroenterology. 2013;29(3):264-70
7. Horvath A, Leber B, Schmerboeck B, Tawdrous M, Zettel G, Hartl A, et al. Randomised clinical trial: the effects of a multispecies probiotic vs. placebo on innate immune function, bacterial translocation and gut permeability in patients with cirrhosis. Aliment Pharmacol Ther. 2016;44(9):926-35
8. Horvath A, Rainer F, Bashir M, Leber B, Schmerboeck B, Gronbaek H, et al. Proton pump inhibitor intake in liver cirrhosis: associations with intestinal dysbiosis, inflammation, permeability and outcome. JAMA. 2018;submitted
9. Bindels LB, Delzenne NM. Muscle wasting: the gut microbiota as a new therapeutic target? Int J Biochem Cell Biol. 2013;45(10):2186-90

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