32

Lower abundance of Clostridium sensu stricto is associated with liver steatosis and fibrosis severity in a prospective cohort of obese patients with metabolic dysfunction-associated fatty liver disease

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Introduction

There is an increasing evidence for the role of the gut microbiota in the pathogenesis of obesity, insulin resistance and metabolic dysfunction-associated fatty liver disease (MAFLD). Deciphering the bacterial signature associated with liver alterations would be interesting as a new indicator for MAFLD pathogenesis.

Aim

Here, we describe the microbiome composition of a cohort of obese patients well characterized for MAFLD severity (i.e. steatosis and fibrosis degree) and link them with other obesity-related extra-hepatic alterations.

Methods

Obese patients recruited prospectively at St-Luc Hospital (FOOD4GUT project) were included. Liver stiffness (LSM) and controlled attenuation parameter (CAP) measurements were performed using liver transient elastography (TE). Physical examination, blood and stool samples and computed tomography (CT) were also assessed. The fecal gut microbiota was analyzed by Illumina sequencing of the 16S rRNA gene.

Results

Stool samples were available for 37 patients. Liver TE allowed us to classify the patients in three groups based on CAP and LSM: LS (low steatosis defined as CAP < 296 dB/m, n=10), HS (high steatosis defined as CAP ≥ 296 dB/m, n=18) and HS+F (high steatosis + fibrosis defined as CAP ≥ 296 dB/m and LSM ≥ 7.8 kPa with M probe or ≥ 6.4 kPa with XL probe, n=9).
Both α- and β- diversity indices of the overall gut microbiota composition were not different between the three groups. Moreover, no changes in the gut microbiota composition were observed at the phylum level between the three groups.
At the taxa level, only Clostridium sensu stricto significantly decreased with the severity of liver steatosis and fibrosis (p=0.021 for HS+F vs HS and p=0.002 for HS+F vs LS).
Microbes discriminant for liver alterations were determined through a pairwise comparison using linear discriminant analysis effect size (LEfSe) analysis. For the LS-HS comparison, Flavonifractor and Faecalibacterium are more represented in the HS group. Regarding the HS and HS+F comparison, we interestingly found that Clostridium sensu stricto characterized the HS group (without fibrosis) whereas Escherichia/Shigella are more represented in the gut microbiota from subjects with fibrosis.
An analysis based on amplicon sequence variants (ASV) revealed 19 bacterial sequences significantly affected according to liver steatosis and/or fibrosis. Among them, Spearman's correlations showed that C. sensu stricto was significantly negatively associated with LSM, CAP, the waist to hip ratio and muscle fat infiltration evaluated by muscle density on CT.

Conclusions

Our study allowed us to elaborate the link between MAFLD severity and extra-hepatic alterations incriminating adiposity, skeletal muscle dysfunction and the gut microbiome. We identified Clostridium sensu stricto as the only genus decreasing with the development of steatosis and fibrosis. This genus also negatively correlated abdominal adiposity and muscle fat infiltration. Those data suggest a gut-liver-muscle axis in the pathogenesis of MAFLD complications.