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Evidence of a clinically relevant relationship between intestinal permeability and microbiome composition in cirrhosis

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Background/Aims: Liver cirrhosis, the10th most common cause of death in the western world, is associated with increased intestinal permeability and alterations of the gut microbiome. However, it is not understood how intestinal permeability and the microbiome are related in cirrhosis. Therefore, we aim to investigate the potential of gut permeability biomarkers to predict mortality and their relation to microbiome composition. Methods/Results: We assessed intestinal permeability by zonulin ELISA in stool in two different study cohorts. In cohort 1 (78 cirrhotic patients) the zonulin dynamics over six months predicted a higher mortality after 24 months of patients whose zonulin levels worsened ($p = 0.048$). In cohort 2 (106 cirrhotic patients) zonulin levels were only available at baseline. In cohort 2 zonulin was able to predict mortality after 42 months ($p = 0.047$). In cohort 1, analysis of 16s rDNA sequencing data with ANCOM and LEfSe showed that Phascolarctobacterium was more abundant in patients with improved zonulin levels. Patients with a higher abundance of Phascolarctobacterium had a better liver function and a lower mortality. Metabolomics analysis showed in cohort 2 that stool acetate levels were lower in patients with high zonulin levels ($p = 0{,}026$). Microbiome analysis in cohort 2 is still pending. Conclusion: Zonulin as a marker of intestinal permeability is able to predict mortality in two different cohorts of cirrhotic patients. Cohort 1 suggests that the predictive power of zonulin might be increased by serial assessment and that microbiome composition and zonulin dynamics are related. The correlation of decreased levels of acetate, one of the most common SCFA produced by gut bacteria, with high zonulin levels further suggest a relationship between microbiome function.