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ASSESSMENT OF PATHOGENIC CHANGES IN THE GUT-LIVER AXIS IN PLWH WITH HEAVY ALCOHOL DRINKING AND GUT DYSBIOSIS MARKED BY DECREASED BUTYROGENIC POTENTIAL

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Abstract:

Purpose: People living with HIV infection (PLWH) experience increasing risk for non-AIDS diseases including liver dysfunction and injury. Both HIV-infection and heavy alcohol drinking (HAD) are known to cause gut microbial dysbiosis and systemic inflammation that may potentially contribute to altered Gut-Liver axis. However, the specific pathogenic features associated with combinatorial harmful effects of alcohol and HIV infection on gut-liver interactions are not completely understood. This study evaluate the pathogenic changes in the Gut-Liver axis in PLWH with HAD.

Methods: Fecal samples and clinical data were obtained from 12 controls (noHIV-noHAD) and 13 PLWH participants with a history of heavy alcohol drinking (HIV-HAD), enrolled in clinical research studies supported by the Southern HIV Alcohol Research at Florida. We (1) performed metagenomics analysis of fecal microbiome employing 16S rRNA gene sequencing on a large-scale Illumina MiSeq platform, (2) assessed plasma biomarkers of intestinal permeability, immune activation and liver dysfunction, and (3) profiled plasma bile acids using a targeted quantitative metabolomics approach employing direct injection mass spectrometry with a reverse-phase LC-MS/MS respectively. Statistical analyses included the non-parametric Mann Whitney test and Spearman correlations.

Data: Metagenomics analysis showed that in comparison to controls, PLWH with HAD have a significant decrease in i) gut microbial diversity (*Firmicutes*/*Bacteroidetes* phyla ratio; $p<0.0001$), ii) largest butyrate producing bacterial family (*Lachnospiraceae;* $p<0.0001$*)* within phylum *Firmicutes* and iii) plasma butyrate levels ($p<0.0001$). Correspondent to the loss in butyrogenic potential, a significant increase in markers of intestinal permeability (IFABP; $p=0.008$) and immune activation (sCD14; $p<0.0001$) was observed. Further, assessment of plasma markers of liver function showed significantly higher levels of homocysteine ($p=0.029$) and increased ratio of secondary bile acid - deoxycholic acid to primary bile acid - cholic acid (DCA/CA; $p=0.006$) in PLWH with AUD compared to control.

Results & Conclusion: Gut microbial dysbiosis involving loss of butyrogenic potential in association with increased intestinal permeability, systemic immune activation and liver metabolic dysfunction, signifies the pathogenic changes in the Gut-Liver axis in PLWH with heavy alcohol drinking.