

A083 Maternal Obesogenic Diet Exposure Leads to Microbiome Associated Changes in Bile Acid Metabolism and Increased Cholestatic Liver Injury in Offspring

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Introduction: We have shown offspring exposed to maternal high fat/high sucrose (HF/HS) diet develop altered bile acid (BA) homeostasis and associated periportal inflammation/fibrosis. The mode of transmission of this phenotype is unclear. The gut microbiome is involved in BA metabolism and is vertically transmitted at birth. We hypothesized that changes in BA homeostasis in HF/HS offspring are mediated by vertical transmission of an altered microbiome. We also evaluated whether HF/HS offspring are more prone to cholestatic liver injury. **Methods:** Female mice were fed chow (CON) or HF/HS diet for 6 weeks and bred with lean males. To evaluate if changes in BA metabolism are microbiome driven, cecal microbiome transplantation (CMT) was performed from CON or HF/HS offspring into antibiotic treated control mice. 16S sequencing was performed to compare the microbiome in HF/HS offspring to CON. BA pool size, intrahepatic BA profile, and gene expression analyses were performed on recipient mice. To induce cholestatic liver injury, ten week old offspring were fed 3,5-diethoxycarbonyl-1,4-dihydrocollidine (DDC) diet for 2 weeks. A group of offspring were subsequently transitioned to chow to recover for 10 days. Tissues were collected for histopathologic analyses. **Results:** Cecal microbiome from HF/HS offspring was different than CON including an increase in Firmicutes to Bacteroidetes ratio and increased Verrucomicrobia. CMT from HF/HS offspring resulted in higher BA pool size in recipient mice compared to CON. Recipients of CMT from HF/HS offspring exhibited increased intrahepatic muricholic acids and decreased deoxycholic acids. After DDC feeding, HF/HS offspring had higher liver weight to body weight ratio, ductular reaction and fibrosis, while macrophage and monocyte infiltration were decreased. After 10 days of recovery, HF/HS offspring exhibited sustained ductular reaction and more periportal fibrosis. **Conclusions:** CMT from HF/HS offspring resulted in an increase in BA pool size and a shift in the intrahepatic BA pool in recipient mice as originally observed in donor HF/HS offspring. This supports a causal role for vertical transfer of an altered microbiome. HF/HS offspring develop increased cholestatic liver injury as well as delayed recovery suggesting blunted hepatobiliary repair. Future studies will focus on the role of vertical transfer of the microbiome to HF/HS offspring in DDC-induced injury and define the mechanisms for delayed hepatobiliary repair.