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MICROBIOTA DYSBIOSIS CONTRIBUTES TO LIVER INJURY IN APOLIPOPROTEIN KNOCKOUT MICE THROUGH THE DISRUPTION OF CHOLESTEROL HOMEOSTASIS

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INTRODUCTION: Our previous studies demonstrated that cholesterol accumulation in liver contributes to the progression of nonalcoholic fatty liver disease (NAFLD). The exact mechanisms of this process have not been completely explained. This study aimed to investigate the effects of gut microbiota on hepatic cholesterol homeostasis in NAFLD.

METHODS: Broad-spectrum antibiotics were used to eliminate gut microbiota in high-fat diet (HFD) induced apolipoprotein E knockout mice. Feces were collected and proportions of microbiota were analyzed by 16S rRNA gene sequencing. Serum lipids were examined by automatic analyzer. Cholesterol accumulation in liver was detected by Oil red O staining, Filipin staining, and intracellular free cholesterol quantitative assay. The expressions of molecules involved in cholesterol homeostasis were measured by immunohistochemical staining and Western blotting.

RESULTS: As demonstrated by 16S rRNA gene sequencing, the abundance of *Desulfovibrio* was significantly increased in HFD mice while the abundance of *Bacteroidetes*, *Ruminococcaceae*, and *Lactobacillus* decreased when compared with the control. Antibiotics treatment effectively depleted gut microbiota in HFD mice. Interestingly, depletion of gut microbiota significantly decreased total cholesterol(TC) and low density lipoprotein(LDL) in the plasma and lipid accumulation in livers of HFD fed mice. Immunohistochemical staining and Western blotting further demonstrated that the expressions of LDL receptor (LDLR) and 3-hydroxy-3-methyl-glutaryl-CoA reductase(HMGR) were downregulated in antibiotics delpleted HFD fed mice.

CONCLUSIONS: Our findings demonstrated that gut microbiota dysbiosis may be responsible for the liver injury in NAFLD by disrupting cholesterol homeostasis. This study provides more evidence for that modification of gut microbita dysbiosis is suggested to be a potential target for NAFLD therapy.