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Metabolism Changes and Biomarker Discovery in Alcohol-Associated Liver Disease

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Alcohol-associated liver disease (ALD) is one of the leading liver diseases, causing millions of deaths globally each year. Liver damage from alcohol is reversible in the early stages without medical intervention. However, due to its asymptomatic nature, ALD often progresses to irreversible liver damage. The current diagnostic methods lack sufficient specificity and sensitivity, and gaps in the overall diagnosis and medical management of ALD remain a challenge. We conducted an untargeted and targeted metabolomics study on urine samples of patients with various stages of ALD. Our data showed that the abundance of 7,9-dimethylamine and seven bile acids can differentiate severe alcoholic hepatitis (AH) from non-severe ALD and non-severe ALD from healthy controls. These results underscore the promise of urinary metabolites as non-invasive biomarkers for ALD diagnosis. We then investigated the metabolic characteristics of the liver of mice with experimental ALD using untargeted metabolomics and lipidomics. We found that the metabolism of polar metabolites was decreased with amino acid metabolism as the most affected pathways. Metabolites involved in glycolysis and the TCA cycle were decreased, while glycerol 3-phosphate (G3P) and long-chain fatty acids were increased. Relative quantification of lipids unveiled an upregulation of multiple lipid classes, suggesting that alcohol consumption drives metabolism toward lipid synthesis. Results from enzyme expression and activity detection indicated that the decreased activity of mitochondrial glycerol 3-phosphate dehydrogenase contributed to the disordered metabolism.