Serum Metabolomic Profiling Identifies Key Metabolic Signatures Associated With Pathogenesis of Alcoholic Liver Disease in Humans

Alcoholic liver disease (ALD) develops in a subset of heavy drinkers (HDs). The goals of our study were to (1) characterize the global serum metabolomic changes in well-characterized cohorts of controls (Cs), HDs, and those with alcoholic cirrhosis (AC); (2) identify metabolomic signatures as potential diagnostic markers, and (3) determine the trajectory of serum metabolites in response to alcohol abstinence. Serum metabolic profiling was performed in 22 Cs, 147 HDs, and 33 patients with AC using ultraperformance liquid chromatography–tandem mass spectrometry. Hepatic gene expression was conducted in Cs (n = 16) and those with AC (n = 32). We found progressive changes in the quantities of metabolites from heavy drinking to AC. Taurine-conjugated bile acids (taurocholic acid [TCA], 127-fold; taurochenodeoxycholic acid [TCDCA], 131-fold; and tauroursodeoxycholic acid, 56-fold) showed more striking elevations than glycine-conjugated forms (glycocholic acid [GCA], 22-fold; glycochenodeoxycholic acid [GCDCA], 22-fold; and glycoursodeoxycholic acid [GUDCA], 11-fold). This was associated with increased liver cytochrome P450, family 7, subfamily B, member 1 and taurine content (more substrates); the latter was due to dysregulation of homocysteine metabolism. Increased levels of GCDCA, TCDCA, GCA, and TCA positively correlated with disease progression from Child-Pugh A to C and Model for End-Stage Liver Disease scores, whereas GCDCA, GCA, and GUDCA were better predictors of alcohol abstinence. The levels of glucagon-like peptide 1 (GLP-1) and fibroblast growth factor (FGF) 21 but not FGF19 were increased in HDs, and all three were further increased in those with AC.

**Conclusion:** Serum taurine/glycine-conjugated bile acids could serve as noninvasive markers to predict the severity of AC, whereas GLP-1 and FGF21 may indicate a progression from heavy drinking to AC.