**METABOLIC PROFILING AS A NONINVASIVE TOOL FOR NONALCOHOLIC STEATOHEPATITIS DIAGNOSIS**

**1 OVERVIEW**

Our understanding of the mechanisms by which nonalcoholic fatty liver disease (NAFLD) progresses from isolated steatosis to steatohepatitis (NASH) is still very limited. Despite the growing number of reports linking the disease with altered serum metabolic levels, an obstacle to the development of metabolome-based NAFLD predictors has been the lack of large cohort data from biopsy-proven patients matched for key metabolic attributes such as obesity. Following a successful pre-clinical study in an animal NAFLD model, we examined the serum metabolic profile of 467 biopsy patients.

**2 NAFLD SERUM METABOLIC PROFILE**

Pre-clinical study in GNMT-KO mice. (left) Glycine-N-methyltransferase (GNMT) deletion leads to steatosis and fibrosis. At 4 months of age micro- and macrovesicular steatosis was observed through the hepatic lobule in GNMT-KO mice. Collagen deposition (serum type III collagen) indicates moderate fibrosis [M. L. Martinez-Chantar et al. Hepatology (2008)]. (right) Principal components analysis of serum metabolic profile [J. Barri et al., J. Prot. Res. (2010)].

**3 OBESITY DEPENDENT NASH BIOMARKERS**

Obesity dependent NASH biomarkers. Mean percent deviations of (a) Sphingolipids, and (b) Oxidized fatty acids in patients diagnosed with NASH as compared to isolated steatosis. Most sphingolipid species were significantly elevated in obesity class III (NASH) compared to lean NASH patients’ sera. Oxidized fatty acids, including both enzymatic (15- and 12-hydroxyeicosatetraenoic acid), proinflammatory (lyso- and phospholipids), and nonenzymatic (5- and 9- and 11-hydroxyeicosatetraenoic acid) oxidation products of arachidonic acid were found elevated in obese NASH patients’ sera.

**4 SERUM METABOLOM-E-WIDE NASH PREDICTOR**

BMI stratified ROC analysis of serum metabolic profile for discrimination between steatosis and NASH patients. (upper) Obesity dependent and lower BMI stratified NASH predictors based on all detected serum metabolites significantly distinguishing steatosis and NASH patients. Cutoff points at maximum average diagnostic accuracy are shown on all plots.

**5 CONCLUSIONS**

- The serum metabolic profile of 467 liver-biopsied individuals had a significant association with liver histology that was dependent on BMI, an observation which indicates that the mechanisms of NASH pathogenesis may be dependent on an individual’s level of obesity.
- Groups of NASH serum metabolite biomarkers include altered other phospholipids, and elevated levels of proinflammatory cytokines in obese patients. Lean NASH patients had significantly reduced levels of serum sphingolipids.
- The present data, indicating that a BMI-dependent serum metabolic profile may reliably distinguish NASH from steatosis patients, have significant implications for the development of NASH biomarkers and potential novel targets for therapeutic intervention.