Widespread dysregulation of metabolic stress pathways is a characteristic of primary biliary cholangitis (PBC): Comparison of the serum metabolomes of PBC patients to matched healthy volunteers

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BACKGROUND & AIM

- Primary biliary cholangitis (PBC) is an autoimmune cholestatic liver disease characterized by progressive inflammation and destruction of intrahepatic bile ducts
- Current analytical methods can measure over 1000 metabolites to define a serum metabolome
- Comparison of the serum metabolomes of patients with PBC to matched healthy volunteers (HV) is a comprehensive approach to discover novel disease signatures and therapeutic opportunities for this disease

METHODS

- Fasting serum samples were collected from 161 PBC patients in a phase 3 study (ENHANCE: NCT03602560) and from 55 healthy volunteers prospectively recruited by matching age, gender and BMI to PBC patients
- Metabolite measurements using UHPLC-MS/MS (Metabolon, Inc.)
  - Untargeted analysis of serum metabolome
  - Targeted analysis of 15 bile acids

Chenodeoxycholic acid (CDCA)	Taurochenodeoxycholic acid (TCDCA)
Cholic acid (CA)	Taurocholic acid (TCA)
Deoxycholic acid (DCA)	Taurodeoxycholic acid (TDCA)
Lithocholic acid (LCA)	Taurolithocholic acid (TLCA)
Glycochenodeoxycholic acid (GCDCA)	Ursodeoxycholic acid (UDCA)
Glycocholic acid (GCA)	Glycoursodeoxycholic acid (GUDCA)
Glycodeoxycholic acid (GDCA)	Tauroursodeoxycholic acid (TUDCA)
Glycolithocholic acid (GLCA)	Total bile acid (TBA)

- The relative abundance of each identified metabolite between PBC patients and HV was evaluated

RESULTS

Demographics and Baseline Characteristics

Demographics	Healthy Volunteers	PBC Patients	PBC Patients' Biochemistry Mean (SD)	
N	55	161	ALP (U/L)	275 (109)
Female, n (%)	52 (95%)	152 (94%)	ALT (U/L)	43 (21)
Age, years	56 (5)	56 (9)	AST (U/L)	37 (15)
BMI, kg/m²	29 (3)	29 (6)	GGT (U/L)	203 (155)
White, n (%)	32 (58%)	145 (90%)	Bilirubin (mg/dL)	0.67 (0.29)
PBC Duration, years	NA	9 (6)	TC (mg/dL)	227 (52)
AMA-positive, n (%)	NA	145 (90%)	LDL-C (mg/dL)	129 (41)
UDCA received, n (%)	NA	153 (95%)	HDL-C (mg/dL)	74 (22)
Cirrhosis, n (%)	NA	17 (11%)	TG (mg/dL)	114 (61)

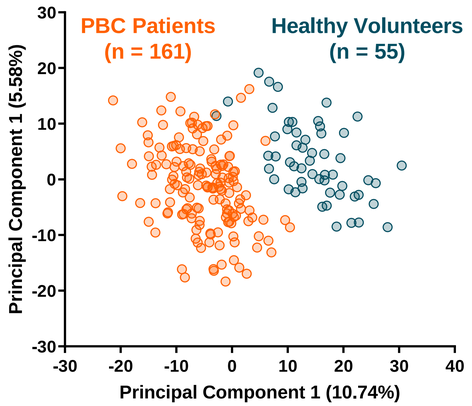
Metabolites: PBC Patients vs. Healthy Volunteers

Untargeted Metabolomic Analysis of Human Serum	
A total of 1031 Metabolites Identified (855 Named and 176 Unnamed)	
PBC Patients vs. Healthy Volunteers	
Total Biochemicals, p ≤ 0.05	653
Biochemicals (Increase | Decrease)	463 | 190

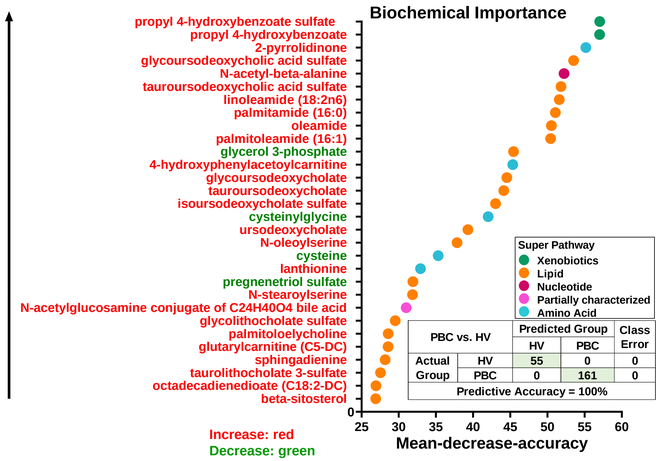
RESULTS

Unique Serum Metabolomic Profile in PBC

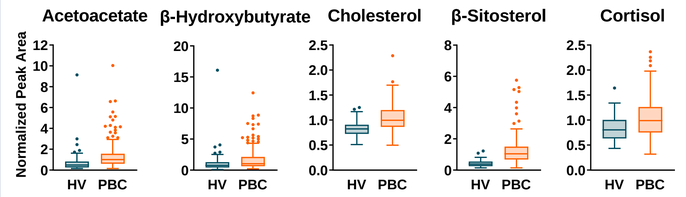
Principal Component Analysis



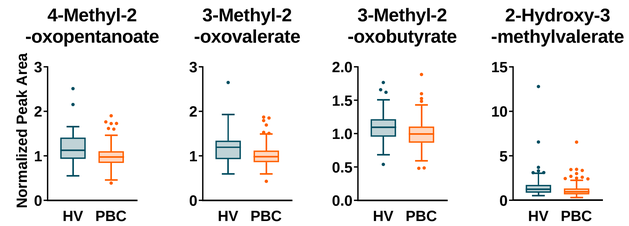
Random Forest



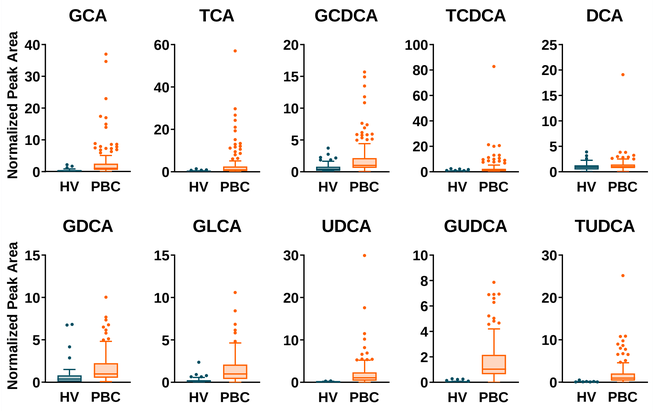
Ketone Bodies, Cholesterol and Cortisol Increased in PBC



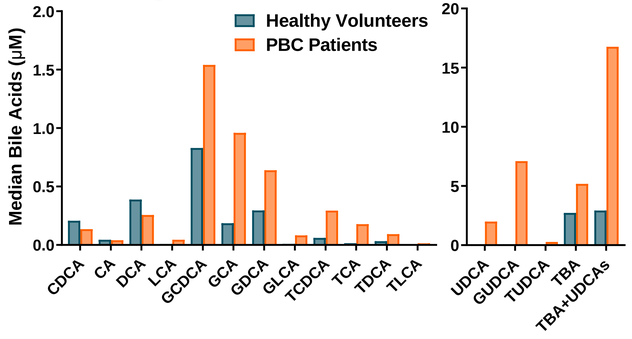
Branched Amino Acid Metabolites Decreased in PBC



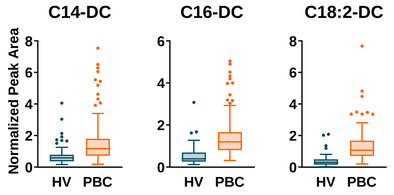
Bile Acids Broadly Increased in PBC



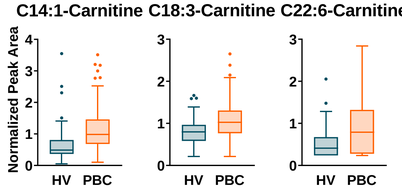
Targeted Metabolomics of Bile Acids



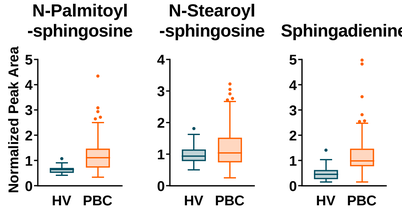
Dicarboxylic Fatty Acids Increased in PBC



Fatty Acylcarnitines Increased in PBC



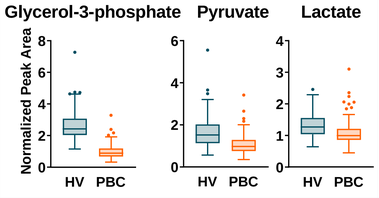
Ceramides and Sphingolipids Increased in PBC



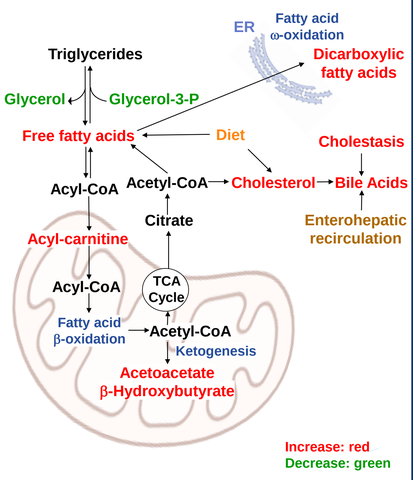
Long-Chain Free Fatty Acids Increased in PBC

Long-Chain Free Fatty Acids		PBC / HV
Myristoleate	C14:1n5	2.18
Pentadecanoate	C15:0	1.60
Palmitoleate	C16:1n7	1.79
Hexadecadienoate	C16:2n6	1.92
10-Heptadecenoate	C17:1n7	1.77
Nonadecanoate	C19:0	1.50
10-Nonadecenoate	C19:1n9	1.68
Docosahexaenoate	C22:6n3	1.73

Glycolytic Intermediates Decreased in PBC



Dysregulated Metabolic Pathways in PBC



CONCLUSION

- PBC patients displayed broad changes in serum metabolites reflective of metabolic stress indicating mitochondrial defects and liver dysfunction associated with their cholestasis
- This new detailed map of metabolomic changes in matched cohorts of significant size sheds light on the broad metabolic pathology of PBC
- These results will aid in our understanding of the substantial impact of PBC on systemic metabolism and energy balance and will help guide efforts to advance therapeutics to counteract the integrated metabolic effects of cholestasis in PBC patients