Untargeted serum metabolomic profiles remain stable over time in large multi-center cohort of >700 outpatients with cirrhosis

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In a multi-center outpatient cirrhosis cohort, serum metabolomic profiles remain stable over time

Introduction

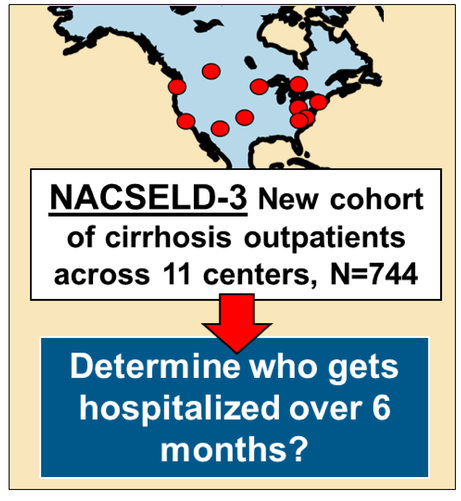
Untargeted metabolomics could be biomarkers for disease progression in cirrhosis but stability over time is unclear. In cirrhosis over time this is important to determine their ability to serve as biomarkers.

Aim

To define differences in serum metabolomics at baseline and changes over time in multi-center outpatient cirrhosis cohort.

Method

NACSELD-3 (North American Consortium for Study of End-Stage Liver Disease) is a multi-center outpatient cirrhosis cohort of compensated (comp) & decompensated (decomp) pts seen at 6M intervals. Clinical & demographic data and serum for metabolomics (done with LC/MS) are collected at each visit. Metabolomic profile at baseline & 6M were compared between/within comp vs decomp groups using paired & unpaired t-tests as appropriate.



Results

We enrolled 744 subjects (285 comp, 459 decomp) from 10 centers of whom 165 comp & 150 decomp were seen again at 6M. All patients' compensated and decompensated status was stable over time.

Between group comparisons: 892 metabolites were different between comp/decomp, of which 500 were higher and 392 were lower in decomp pts. At 6M, 676 metabolites were different, of which 350 were higher & 326 were lower in decomp pts. These comparisons were consistent at both timepoints apart from 8 metabolites. *8 metabolites changed direction from baseline to 6M between comp/decomp pts*: 2-ketocaprylate (0.81 to 1.36-fold), indole propionate (0.98 to 1.05), 2-aminooctanoate (0.9 to 1.47), N-methylhydroxyproline (0.85 to 1.24) & glycodeoxycholate (0.91 to 1.31) were lower in decomp vs comp at baseline but flipped i.e., increased at 6M post. The reverse (higher at baseline & lower at 6M in decomp) was seen with glycoursodeoxycholate (1.2 to 0.71), 5-hydroxyindole sulfate (1.23 to 0.69) & tauroursodeoxycholate sulfate (1.09 to 0.3).

Within group analysis: *Compensated*: 130 metabolites differed of which 95 ↑ & 35↓ at 6M vs baseline. Those that reduced at 6M were biliverdin, vitamin C/E metabolites, long-chain fatty acids, phosphocholines, sex steroids, & tauro/glycoursodeoxycholate sulfate. Those that ↑ were amino acid derivatives related to urea cycle (arginosuccinate) & protein breakdown, bioenergetics (aconitate, malate, citrate) & hormones (cortisol).

Decompensated: 66 metabolites changed (37↑/29↓) at 6M vs baseline. Those that ↓were biliverdin, long chain FAs, carnitine derivatives, & serotonin. Metabolites that ↑ were again amino acid derivatives & urea cycle intermediates (citrulline, ornithine), GABA derivatives (imidazole acetate), short/medium fatty acids (butyrate, valerate) & N-acetylated amino acids that are linked with renal disease

Conclusions

Serum metabolomics are largely stable over time in outpatients with cirrhosis in a multi-center study across North America, which encourages their use as biomarkers. Few metabolites that changed differentially were microbially modified metabolites (bile acids, indoles, short chain fatty acids), long-chain fatty acids, and urea cycle intermediates.

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