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Significant Alteration of the Portal Circulation in Over Half of the Chronic HCV Patients with Ishak Fibrosis Stage F0-F2

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Introduction: Approximately 40% of patients with chronic hepatitis C (CHC) have minimal disease as defined by Ishak fibrosis stages F0 to F2. A subset of F0-F2 patients, presumably with hepatic impairment, progress to cirrhosis and clinically decompensate. In this study we sought to identify the high risk subset by quantifying hepatic impairment using noninvasive quantitative tests.

Methods: Patients with CHC and Ishak F0-F2 (n=21) were recruited from our Hepatology Clinic and compared to healthy control subjects (n=32). All were assessed by standard laboratory tests and metabolic tests including caffeine elimination, antipyrine clearance, galactose elimination capacity, and formation of MEGX from lidocaine. The portal circulation was quantified by the clearance of orally administered cholate-d4 (FLOW), the ratio of the clearances of intravenous cholate-13C to oral cholate-d4 (SHUNT), and serum cholate-d4 at 60 min (STAT). Labeled cholates were assayed by an LCMS method validated for accuracy and precision. As CHC progresses, FLOW, which assesses the portal blood flow, is reduced while SHUNT, which assesses portal-systemic shunting, is increased. STAT, which uses a single blood sample to infer the impaired FLOW, is also increased.

Results: Within the F0-F2 patient group, 62% had normal ALT, 95% had normal bilirubin, 95% had normal INR, and 71% had normal albumin. All the metabolic tests failed to detect hepatic impairment in F0-F2 patients. However the F0-F2 patients had significantly lower FLOW, higher SHUNT, and higher STAT (Table 1). ROC analysis of the test results for all subjects was used to determine the optimum cutoffs that distinguished the F0-F2 patients from the controls and that defined hepatic impairment for each test.

Conclusions: Over 50% of CHC patients with F0-F2 disease have significant alteration of the portal circulation which can be uniquely quantified by FLOW, SHUNT, and STAT. Hepatic impairment may define the subset of F0-F2 patients who have the greatest need for antiviral treatment.

Test results for controls and CHC F0-F2 are the mean +/- SD.

Test	Controls	CHC F0-F2	p value	ROC c-statistic	Cutoff	Sensitivity	Specificity
FLOW (mL/min/kg)	30+/-9	20+/-6	0.00003	0.81	20.3	57%	88%
SHUNT (%)	19+/-5%	26+/-7%	0.0008	0.75	25.2%	52%	88%
STAT (µM)	0.38+/-0.13	0.64+/-0.13	0.0005	0.73	0.52	52%	91%