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Hepatic short chain fatty acid (SCFA) oxidation in nonalcoholic fatty liver disease

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Reduced fat oxidation in liver mitochondria is hypothesized to be a primary cause of excess liver fat and tissue injury in nonalcoholic fatty liver disease (NAFLD). A definitive test of this hypothesis currently requires a liver biopsy to obtain tissue for mitochondrial isolation and in-vitro testing. The goal of the study was to develop a noninvasive method to investigate liver fat oxidation in humans. To accomplish this, we chose to utilize the SCFA octanoate because it is uniquely cleared by the liver and enters the mitochondria without need for a carrier protein. For the breath test, stably-labeled, ^{13}C-octanoate (23.4 mg) was fed in orange juice and breath samples collected 8 times over a 135-minute period. Total CO_2 production rate was measured by respiratory gas analysis (Parvo Medics) and $^{13}CO_2$ enrichment assessed by isotope-ratio mass-spectrometry (IR-MS). 12 NAFLD patients (4 men, 8 women, 44$\pm$3 years) underwent diagnostic liver biopsy and liver tissues were scored histologically by a pathologist to determine the level of liver disease (NAFLD activity score: 0, (healthy) to 8, (cirrhosis)). In addition, six patients participated in a 9-month, lifestyle treatment program followed by a repeat liver biopsy. Data from the $^{13}CO_2$-breath test was compared to the NAFLD score. Preliminary results from two of the lifestyle-treated subjects available so far demonstrated greater fat oxidation after treatment. Ongoing work will complete the analysis of data from the other subjects. Octanoate oxidation data will be compared to liver histology, the NAFLD score, liver fat measured by MRI, body composition assessed by DEXA, blood concentration of metabolites, and whole-body fat oxidation calculated using the respiratory quotient. Using a direct comparison to data from isolated liver tissue in humans, this method will be the first evaluation of the efficacy of an in-vivo breath test that quantitates liver fat oxidation in patients with NAFLD.