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Fatty acid oxidation in nonalcoholic steatohepatitis (NASH)

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A major component in the pathogenesis of NASH is reduced hepatic mitochondrial activity, specifically decreased β-oxidation β-ox). The diagnosis of NASH requires a liver biopsy for histologic grading of liver tissue. In the present study, 18 subjects (6 men, 12 women, 47±8 years, 119±23kg (mean±SD)) underwent a diagnostic liver biopsy to confirm NASH; liver tissues were scored by a pathologist to determine liver disease status, denoted by the NAFLD activity score (NAS). This project's goal was to quantify hepatic β-ox using a noninvasive breath test to predict NASH severity. We utilized the stably-labeled fatty acid 1,2,3,4-^{13}C-octanoate. In theory, when fed orally, subsequent breath $^{13}CO_2$ levels reflect hepatic β-ox, because octanoate is directly transferred to the liver via the portal vein and enters the mitochondria without a carrier protein. A single dose of ^{13}C-octanoate (23.4mg) was fed in orange juice and eight breath samples were collected once before and intermittently for 135-minutes. Total CO_2 production rates were measured by respiratory gas analysis and breath $^{13}CO_2$ enrichment measured by isotope ratio-mass spectrometry. During the test, subjects oxidized an average of 24±4% (range: 17-31%) of the octanoate dose. Baseline octanoate oxidation did not correlate with body weight, liver enzymes, NAS, or fibrosis. After nine months, 11 of the subjects underwent a second biopsy to reassess their liver disease and repeated the breath test. The change in steatosis (a NAS sub-score) was associated with changes in octanoate oxidation – both in units of absolute $^{13}CO_2$ produced ($r=-0.523$, $P=0.012$) and total oxidized relative to body weight ($r=-0.707$, $P=0.001$). These results suggest that a ^{13}C-octanoate breath test alone is not a sufficient indicator of liver disease. However, the results support ^{13}C-octanoate breath tests as a strong predictor of changes in steatosis in NASH and repeated breath tests as an indicator of change in liver disease status..