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

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BACKGROUND

- 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)
- Since 2017, The Parks Lab has been conducting a weight loss study with the specific aim of improving liver health and functioning
  - Phase I: Participants suspected to have NAFLD are scheduled for a medically indicated liver biopsy, which undergoes histologic grading, for diagnosis of their disease.
    - Patients with advanced liver disease (scoring ≥4/8) are eligible for phase II.
  - Phase II: 9-month diet and exercise treatment program intended to cause weight loss and improve liver health.
    - There are 8 visits to track participant progress by measuring blood lipid concentrations, weight changes, exercise tolerance, and ad libitum movement.
- Participants include overweight men and women who range in age (43±3) who have been diagnosed with NAFLD or the more advanced condition nonalcoholic steatohepatitis (NASH).

HYPOTHESIS

The goal of the present study was to develop a noninvasive method to investigate liver fat oxidation in humans.

METHODS

To develop the method, we chose to utilize the short chain fatty acid (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). Nine NAFLD patients (4 men, 5 women, 44±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, five 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 five of the lifestyle-treated subjects available so far demonstrated greater fat oxidation after treatment. Current work is ongoing to complete the analysis of data from the other subjects. The 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.

Table 1. Subject Characteristics

mean ± SD	Healthy Range	Baseline (n = 5)	Follow-Up (n = 5)
Age (y)		44 ± 4	
Weight (kg)		123.6 ± 4.9	112.1 ± 4.0*
BMI (kg/m^2)		41.6 ± 2.6	38.3 ± 2.2
AST (mg/dL)	< 32	90 ± 38	23 ± 2*
ALT (mg/dL)	< 34	88 ± 32	31 ± 4*
Liver Weight[1] (kg)		1.8 ± 0.1	1.6 ± 0.1*
Body fat %		42% ± 9%	41% ± 7%
NAS	0 - 1	6.6 ± 0.9	3.5 ± 2.5
Fibrosis score	0 - 1	1.0 ± 1.4	1.0 ± 0.7

* indicates $P < .05$

SHORT CHAIN FATTY ACID OXIDATION

Figure 1. Theoretical pathway of short chain fatty acid oxidation

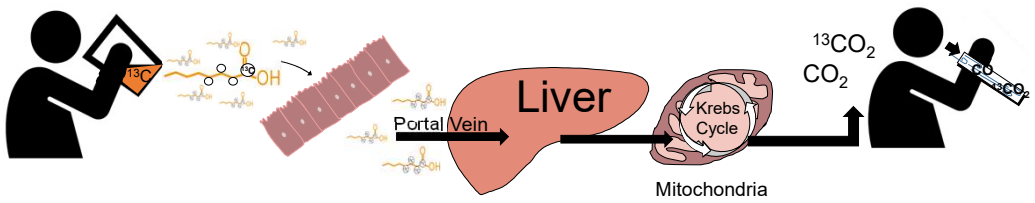


Figure 2a. Baseline $^{13}CO_2$% excess **Figure 2b. Follow-Up $^{13}CO_2$% excess**

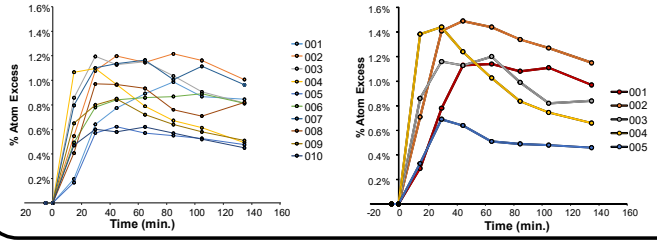
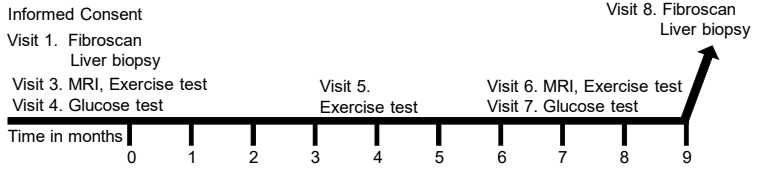
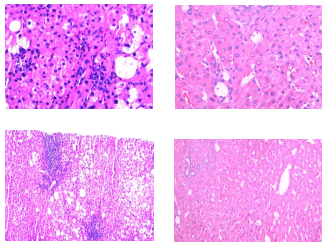


Figure 3. Study Design



HISTOLOGY

Figure 4. Subject #2 liver histology



RESULTS

Figures 5 - 6. Liver biopsy results

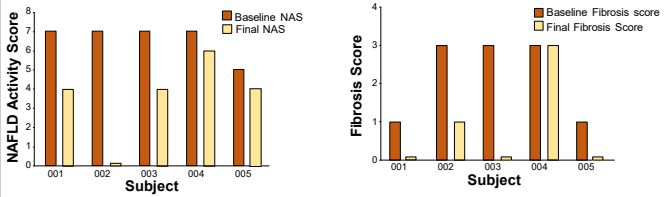
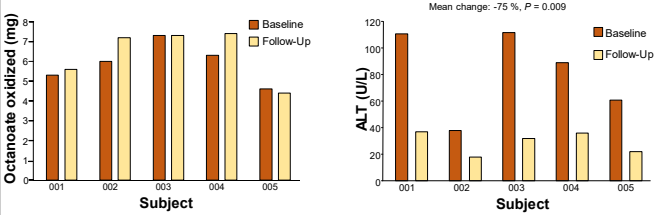


Figure 7. Octanoate oxidized

Figure 8. ALT (U/L)



RELATIONSHIPS BETWEEN SCFA and LIVER FAT

Figure 9. Absolute change in octanoate oxidized vs. change in body fat

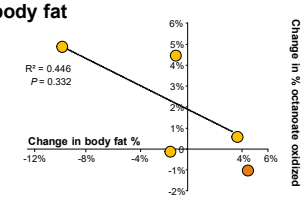


Figure 10. Relative change in oxidized octanoate vs. change in estimated liver weight (ESLW)[1]

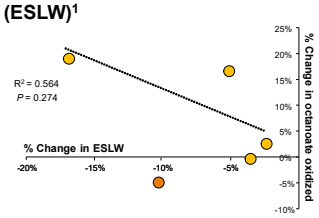
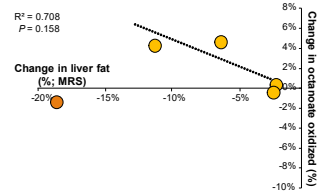


Figure 11. Absolute change in octanoate oxidized vs. change in liver fat



CONCLUSION

Short chain fatty acid oxidation tends to increase with improvement of other liver health indicators, such as liver enzymes, NAFLD activity score (NAS), and liver fat, as assessed by MRI. Large variation between individuals proves to be a limitation as results from five patients are not generalizable to an entire population. Future directions for the study involve recruitment of more patients to continue the present study.

1. Chan, S. C., Liu, C. L., Lo, C. M., Lam, B. K., Lee, E. W., Wong, Y., & Fan, S. T. (2006). Estimating liver weight of adults by body weight and gender. *World Journal of Gastroenterology, 12*(14), 2217. doi: 10.3748/wjg.12.2217

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