"Fatty acid dysregulation in NAFLD"

STOPNASH
Symposium on the Origins and Pathways of Nonalcoholic Steatohepatitis
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Studying the fasting to fed state transition

The ability to appropriately fast is maintained in obesity and insulin resistance.

The metabolism that causes disease occurs at the transition from the fasting to fed state.

Outline

• Lipogenesis in health subjects and those with insulin resistance:
  - effect of sugars
  - circadian patterns

• Is liver energy metabolism limited in NAFLD?

• Changes in fatty acid fluxes with weight loss in NAFLD

• A case study of weight loss
Liver-TG fatty acid sources, fluxes, and fates

Liver’s synthesis of de novo fatty acids from dietary CHO

Elevated lipogenesis: Obesity, insulin resistance, diabetes
Constant, elevated lipogenesis in Caucasian NAFLD patients

NAFLD Clinical Trial

• A study of subjects with a wide range of liver fat and insulin sensitivities

• To determine the relationships between nutrient metabolism during the fasted and fed states and liver (and whole body) fatty acid flux.

• Determine the metabolic mechanisms that reduce liver fat during weight loss.

Subject characteristics

<table>
<thead>
<tr>
<th></th>
<th>Low IHTG</th>
<th>High IHTG</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of subjects</td>
<td>11</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>IHTG (%)</td>
<td>3.1 ± 2.9</td>
<td>18.4 ± 3.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>35.3 ± 7.8</td>
<td>34.9 ± 5.3</td>
<td>0.443</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>102.9 ± 21.8</td>
<td>92.2 ± 17.5</td>
<td>0.193</td>
</tr>
<tr>
<td>Body fat (%)</td>
<td>39.7 ± 10.5</td>
<td>39.2 ± 6.8</td>
<td>0.442</td>
</tr>
<tr>
<td>FFA (mmol/L)</td>
<td>0.57 ± 0.15</td>
<td>0.66 ± 0.12</td>
<td>0.106</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>110 ± 50</td>
<td>134 ± 54</td>
<td>0.137</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>91.3 ± 8.8</td>
<td>98.0 ± 14.4</td>
<td>0.195</td>
</tr>
<tr>
<td>Insulin (mU/L)</td>
<td>8 ± 4</td>
<td>11 ± 4</td>
<td>0.049</td>
</tr>
<tr>
<td>HOMA</td>
<td>1.67 ± 0.79</td>
<td>2.63 ± 1.10</td>
<td>0.024</td>
</tr>
<tr>
<td>SI (10⁻⁴ min⁻¹ per μU/mL)</td>
<td>3.1 ± 1.4</td>
<td>2.2 ± 1.4</td>
<td>0.136</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>47 ± 36</td>
<td>69 ± 45</td>
<td>0.239</td>
</tr>
</tbody>
</table>
Higher de novo lipogenesis in NAFLD.
Less suppression with fasting.

TRL-TG from lipogenesis

Obese control

Significantly lower than 1 AM

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de novo lipogenesis and dietary sugars

Dietary total sugars
21.1 ± 1.3%
P = 0.001

Dietary total sugars
5.6 ± 0.8%
P = 0.030

P = 0.001

Dietary total sugars
21.1 ± 1.3%
P = 0.001

Dietary total sugars
5.6 ± 0.8%
P = 0.030

High IHTG

Low IHTG

Lipogenesis (% of TRL-TG fatty acids)

P = 0.030

21.1 ± 1.3%

5.6 ± 0.8%
The role of mitochondrial energy metabolism

Current controversy

Few mitochondria in NAFLD?
More mitochondria, but dysfunction?
ROS?

Liver TCA cycle activity

Sunny/Parks, Cell Metabolism, 2011
Is mitochondrial activity limiting in NAFLD?

Fasting hepatic substrate fluxes in humans

Yes, energy generation is limited

No, energy metabolism is not limited

Plasma α-PB concentrations as a biomarker? just don’t do it.
Hepatic energy metabolism

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Phase 1
Baseline metabolic tests

Phase 2
Weight loss and follow-up
Changes due to caloric restriction

<table>
<thead>
<tr>
<th>BW (kg)</th>
<th>Baseline</th>
<th>Post WL</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>51</td>
<td>30</td>
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</tbody>
</table>

> < 30 U/L normal

Plasma ALT (U/L)

Post Wt-Loss

P = 0.006

Baseline

51

10

20

30

40

50

60

70

< 5.6% normal

Liver-TG by MRS

Post Wt-Loss

Baseline

P = 0.002

0%

2%

4%

6%

8%

10%

12%

14%

16%

< 5.6% normal

Insulin Sensitivity

Baseline

Post Wt-Loss

P = 0.03

0

2

4

6

8

10

12

14

16

18

20

Fasting and fed concentrations

<table>
<thead>
<tr>
<th>Hours relative to midnight</th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
<th>12</th>
<th>14</th>
<th>16</th>
<th>18</th>
<th>20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose (mg/dL)</td>
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<tr>
<td>FFA (mmol/L)</td>
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<tr>
<td>Plasma TG (mg/dL)</td>
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</tbody>
</table>

VLDL-TG TG Sources (mmol/L)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>PostWL</th>
<th>Baseline</th>
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</thead>
<tbody>
<tr>
<td>DNL</td>
<td>0.544</td>
<td>0.411</td>
</tr>
<tr>
<td>FFA</td>
<td>0.527</td>
<td>0.411</td>
</tr>
<tr>
<td>EvMeal</td>
<td>0.524</td>
<td>0.411</td>
</tr>
</tbody>
</table>

P = 0.004

P = 0.527

P = 0.057

P = 0.524

P = 0.057

P = 0.524
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Case Study: Subject #8

33 yo Hispanic female

Body weight = 68.8 kg
BMI = 31.8 kg/m²
Body fat = 40.7%
W:H = 0.99
Liver fat = 27.3%

Glucose = 93 mg/dL
Insulin = 11 mU/L
HbA1c = 6.2%
ALT = 63 mU/L

Subject #8 Histology

1. Baseline Histology
2. Follow-up Histology

Baseline
Body weight: 68 kg
Liver fat: 27.3%
Plasma ALT: 63 U/L

Follow-up
Body weight: 61.5 kg
Liver fat: 1.8%
Pulasma ALT: 11 U/L

Liver histology:
- Mild pericellular fibrosis adjacent to central veins.
- Ballooning degeneration of hepatocytes.

Baseline Histology
- Healthy liver demonstrating resolution of inflammation and fibrosis.
Summary

Metabolic derangements of the fasted to fed state transition lead to the development of disease.

These preliminary data suggest that the metabolic environment of the liver in metabolic syndrome is characterized by an increase in lipogenesis from sugars.

Weight loss significantly lowers liver fat content. It can do so by improving all of these pathways to reduce the burden of fatty acids in the liver.

Of the 22 outcomes measured, the primary improvement in patients regressing their liver fat was a significant reduction in hepatic de novo lipogenesis.

Parks Lab motto, "Panta Rhei"
~ all things are in flux ~

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Environmental weight loss strategy