Rapid and body weight-independent improvement of endothelial and high density lipoprotein function after Roux-en-Y gastric bypass: Role of Glucagon-like preptide-1

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Bariatric surgery reduces cardiovascular morbidity and mortality

Bariatric surgery (RYGB) is the **only effective** treatment against severe obesity (BMI > 35 Kg/m²)

-long lasting weight loss **15-35%**

Diabetes improves **immediately (days)** after bariatric surgery, before any significant weight loss

Umeda LM et al, Obes Surg 2011
Pournaras D et al, Ann Surg 2010
Sjöström L et al., NEJM 2004; JAMA 2014
How does this happen?

**RYGB/VSG**
- Change Gut Physiology

**Modulation**
- GUT Hormones

**Benefits**
- Whole Body

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**Roux-en-Y Gastric Bypass**

César Roux (1857-1934)

**Glucagon Like Peptide-1 (GLP-1) increase after RYGB**

Patti MA et al. Obesity 2009
Jørgensen NB et al Diabetes 2013

Glucagon-like peptide (GLP1) has pleiotropic cardio-metabolic actions

Campbell, J. et al Cell Metabolism. 2013
Rapid and body weight-independent improvement of endothelial and high-density lipoprotein function after Roux-en-Y gastric bypass:
role of glucagon-like peptide-1.

Osto E. et al. Circulation 2015; 131:871-881
**Study design**

**A. Rat model**

- **Surgery**
  - 7 weeks of high fat (60% kcal fat) + high cholesterol (1.25%) diet
  - liraglutide: 0.2mg/kg 2xS.C. Inj; exendin 9: 10ug/kg/h minipumps

- **8 days**
  - controls + liraglutide
  - body-weight-matched
  - RYGB
  - RYGB + exendin9-39

- **Harvesting**
  - endothelial function
  - HDL properties evaluation

**B. 29 Patients**

- **28 Healthy -29 BMI-matched to 12 weeks**

- **Fasting blood sampling:**
  - (D0) RYGB
  - (D14) 14 days
  - (12 weeks) 12 weeks

- **-HDL properties evaluation**
### Results

<table>
<thead>
<tr>
<th></th>
<th>D0</th>
<th>RYGB D14 (n=29)</th>
<th>12W</th>
<th>BMI-matched to 12W RYGB (n=29)</th>
<th>Healthy (n=28)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GLP-1, pg/ml</strong></td>
<td>0.70±0.11</td>
<td>3.88±0.49&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2.3±0.42&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td>1.5±1.9</td>
</tr>
<tr>
<td><strong>Bile acids, umol/L</strong></td>
<td>8.23±0.49&lt;sup&gt;a&lt;/sup&gt;</td>
<td>9.40±0.53&lt;sup&gt;a&lt;/sup&gt;</td>
<td>11.79±0.75&lt;sup&gt;bc&lt;/sup&gt;</td>
<td></td>
<td>12.09±0.73</td>
</tr>
<tr>
<td><strong>Glucose, mmol/L</strong></td>
<td>6.40±0.25&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5.39±0.11&lt;sup&gt;b&lt;/sup&gt;</td>
<td>5.12±0.11&lt;sup&gt;b&lt;/sup&gt;</td>
<td>5.49±0.27</td>
<td>5.29±0.15</td>
</tr>
<tr>
<td><strong>Insulin, u UI/ml</strong></td>
<td>19.91±2.87&lt;sup&gt;a&lt;/sup&gt;</td>
<td>13.49±1.48&lt;sup&gt;ab&lt;/sup&gt;</td>
<td>11.60±1.48&lt;sup&gt;b&lt;/sup&gt;</td>
<td>13.91±1.64</td>
<td>6.18±1.0</td>
</tr>
<tr>
<td><strong>HOMA IR</strong></td>
<td>2.62±0.34&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.81±0.16&lt;sup&gt;ab&lt;/sup&gt;</td>
<td>1.44±0.16&lt;sup&gt;bc&lt;/sup&gt;</td>
<td>1.81±0.21</td>
<td>0.82±0.14</td>
</tr>
</tbody>
</table>

*Osto E et al. Circulation 2015*
Endothelial vasorelaxation

Pre-incubation with L-NAME completely inhibited the relaxation induced by both insulin and GLP-1.
- reduced oxidative stress,
  increased aortic NO bioavailability

- GLP-1-dependent signaling was selectively activated in rat aortae after RYGB independently from weight loss and was mimicked by liraglutide treatment

Osto E et al. Circulation 2015
A certain degree of weight and BMI is not sufficient or critical per se to improve the protective properties of HDL.

Osto E et al. Circulation 2015
The superior benefits of bariatric surgery compared to current conservative management likely result from the influence of surgery on several cardio-metabolic aspects. Some of these may be GLP-1 mediated.

Understanding how bariatric surgery leads to these cardio-metabolic benefits may help to design novel therapeutic strategies against morbid obesity and in particular its severe cardiovascular risk.
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Thank you for your attention!