Cardiology Update
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Bariatric surgery in obesity and type 2 diabetes

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I will not discuss off label use and/or investigational use in my presentation
I do not have financial relationship to disclose
The problem

Obesity and type 2 diabetes are epidemic

anti-obesity medications offer 5-10% body weight loss

Lifestyle interventions deliver on average a 7% body weight loss

Flegal KM et al. JAMA. 2013;309:71-82

The problem

Cardiovascular events in overweight or obese with type 2 diabetes were not reduced over a maximum follow-up of 13.5 years.
Bariatric Surgery

Swedish Obese Subjects (SOS) study

The average body weight loss after surgery varies from 15% to 35% depending on the procedure used.

Efficacy

Maintenance

Sjöström L et al., NEJM 2004
Bariatric surgery reduces cardiovascular morbidity and mortality

the magnitude of the cardiovascular risk factors reduction in the short to medium term after bariatric surgery exceeds the effect of weight loss itself

Sjöström et al JAMA 2012

Vest AR et al Circulation. 2013
Metabolic surgery

Glycemia, insulin secretion and sensitivity is restored immediately after bariatric surgery, before any significant body weight loss.

Umeda LM et al., Obes Surg 2011
Pournaras D et al, Ann Surg 2010
Randomized controlled evidence

At 2 years, diabetes remission in no patients on medical-therapy versus 75% after gastric-bypass and 95% in the biliopancreatic-diversion group.

Type 2 diabetes mellitus improves through various mechanisms beyond reduced food intake and body weight loss.

Rubino et al. Annu. Rev. Med. 2010
Who Would Have Thought It?
An Operation Proves to Be the Most Effective Therapy for Adult-Onset Diabetes Mellitus

From a gastrointestinal operation that was designed to promote only weight loss to

Metabolic surgery

Rubino et al. Annu. Rev. Med. 2010
The beneficial effects likely derive from the unique anatomical gut re-arrangement and the altered flow of nutrients after RYGB rather than simply from weight loss.
After RYGB, the modified entero-hepatic circulation of bile acids increases their intraluminal and systemic concentrations.

Elevated levels of bile acids may modify the release of gastrointestinal hormones and in particular Glucagon like peptide 1.
Mechanisms

plasma fasting and postprandial levels of GLP-1 increase rapidly after RYGB,

Umeda LM et al., Obes Surg 2011

but not after dietary restriction, despite a similar weight loss

Laferriere B et al J Clin Endocrinol Metab 2008
glucagon-like peptide (GLP1) has pleiotropic cardio-metabolic actions

Campbell, J. et al Cell Metabolism. 2013

endothelial vasorelaxation

HDL synthesis and efflux
Aim

to investigate the rapid effects of RYGB on obesity-induced endothelial and HDL dysfunction and whether GLP-1 has a role in these effects
**Study design**

**A. Rat model**

- **Surgery**
  - sham-operated ad libitum fed=controls
  - controls + liraglutide
  - body-weight-matched
  - 8 days
  - harvesting

  - RYGB
  - RYGB + exendin9-39

- 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

- 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>GLP-1, pg/ml</td>
<td>0.70±0.11</td>
<td>3.88±0.49b</td>
<td>2.3±0.42b</td>
<td></td>
<td>1.5±1.9</td>
</tr>
<tr>
<td>Bile acids, umol/L</td>
<td>8.23±0.49a</td>
<td>9.40±0.53a</td>
<td>11.79±0.75bc</td>
<td></td>
<td>12.09±0.73</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>6.40±0.25a</td>
<td>5.39±0.11b</td>
<td>5.12±0.11b</td>
<td>5.49±0.27</td>
<td>5.29±0.15</td>
</tr>
<tr>
<td>Insulin, u UI/ml</td>
<td>19.91±2.87a</td>
<td>13.49±1.48ab</td>
<td>11.60±1.48b</td>
<td>13.91±1.64</td>
<td>6.18±1.0</td>
</tr>
<tr>
<td>HOMA IR</td>
<td>2.62±0.34a</td>
<td>1.81±0.16ab</td>
<td>1.44±0.16bc</td>
<td>1.81±0.21</td>
<td>0.82±0.14</td>
</tr>
</tbody>
</table>

Osto E et al. Circulation 2015
Pre-incubation with L-NAME completely inhibited the relaxation induced by both insulin and GLP-1.
In obese rat, RYGB rapidly
(1) reduced oxidative stress, increased aortic NO
bioavailability
(2) GLP-1-dependent signaling was selectively activated
in rat aortae after RYGB independently from weight
loss and was mimicked by liraglutide treatment.
In obese rat, RYGB rapidly improved endothelial protective properties of HDL

Osto E et al. Circulation 2015
# Clinical Characteristics in patients and healthy subjects

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</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td>40.9 ± 1.7</td>
<td>124.0 ± 3.4 b</td>
<td>109.3 ± 3.4 abc</td>
<td>110.3 ± 3.8 abc</td>
<td>66.0 ± 1.8</td>
</tr>
<tr>
<td><strong>Female gender, n (%)</strong></td>
<td>17 (58.6%)</td>
<td>19 (65%)</td>
<td>14 (50%)</td>
<td>14 (50%)</td>
<td></td>
</tr>
<tr>
<td><strong>Height, m</strong></td>
<td>1.7 ± 0.01</td>
<td>1.7 ± 0.01</td>
<td>1.7 ± 0.01</td>
<td>1.7 ± 0.01</td>
<td></td>
</tr>
<tr>
<td><strong>Body weight, kg</strong></td>
<td>134.0 ± 3.7 a</td>
<td>124.0 ± 3.4 b</td>
<td>109.3 ± 3.4 abc</td>
<td>110.3 ± 3.8 abc</td>
<td>66.0 ± 1.8</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td>45.4 ± 1.0 a</td>
<td>42.2 ± 1.0 b</td>
<td>37.0 ± 1.0 abc</td>
<td>37.15 ± 0.9</td>
<td>21.9 ± 0.3</td>
</tr>
<tr>
<td><strong>Current smokers (%)</strong></td>
<td>5/29 (17%)</td>
<td>4/29 (14%)</td>
<td>3/29 (10%)</td>
<td>5/29 (17%)</td>
<td></td>
</tr>
<tr>
<td><strong>Diabetes, n (%)</strong></td>
<td>6/29 (20.7%)</td>
<td>4/29 (13.8%)</td>
<td>0/29 b (0%)</td>
<td>2/29 (6.9%)</td>
<td></td>
</tr>
<tr>
<td><strong>OSAS</strong></td>
<td>9/29 (31.0%)</td>
<td>7/29 (24.1%)</td>
<td>6/29 (20.7%)</td>
<td>10/29 (34.5%)</td>
<td></td>
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</tbody>
</table>

## Lipid profile

<table>
<thead>
<tr>
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<th>D0 (n=29)</th>
<th>RYGB D14 (n=29)</th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Total cholesterol (mmol/l)</strong></td>
<td>4.8 ± 0.2</td>
<td>4.2 ± 0.2 b</td>
<td>4.0 ± 0.1 ab</td>
<td>5.10 ± 0.20</td>
<td>4.89 ± 0.10</td>
</tr>
<tr>
<td><strong>LDL (mmol/l)</strong></td>
<td>3.0 ± 0.1</td>
<td>2.6 ± 0.1 b</td>
<td>2.4 ± 0.1 b</td>
<td>309 ± 0.19</td>
<td>2.8 ± 0.16</td>
</tr>
<tr>
<td><strong>HDL (mmol/l)</strong></td>
<td>1.0 ± 0.1 a</td>
<td>0.8 ± 0.05 ab</td>
<td>1.0 ± 0.1 ac</td>
<td>1.19 ± 0.04</td>
<td>1.62 ± 0.10</td>
</tr>
<tr>
<td><strong>LDL/HDL</strong></td>
<td>3.14 ± 0.23 a</td>
<td>3.35 ± 0.24 a</td>
<td>2.70 ± 0.16 abc</td>
<td>2.65 ± 0.19</td>
<td>1.87 ± 0.19</td>
</tr>
<tr>
<td><strong>TG (mmol/l)</strong></td>
<td>1.72 ± 0.13 a</td>
<td>1.80 ± 0.12 a</td>
<td>1.45 ± 0.06 ac</td>
<td>2.47 ± 0.29</td>
<td>0.95 ± 0.08</td>
</tr>
</tbody>
</table>

## Medications

<table>
<thead>
<tr>
<th></th>
<th>D0 (n=29)</th>
<th>RYGB D14 (n=29)</th>
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<th>BMI-matched to 12W RYGB (n=29)</th>
<th>Healthy (n=28)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Metformin, n (%)</strong></td>
<td>3/29 (10.3%)</td>
<td>2/29 (6.9%)</td>
<td>0/29 (0%)</td>
<td>2/29 (6.9%)</td>
<td></td>
</tr>
<tr>
<td><strong>ACEI (%)</strong></td>
<td>2/29 (6.9%)</td>
<td>2/29 (6.9%)</td>
<td>0/29 (0%)</td>
<td>1/29 (3.4%)</td>
<td></td>
</tr>
<tr>
<td><strong>Sartans</strong></td>
<td>2/29 (6.9%)</td>
<td>2/29 (6.9%)</td>
<td>2/29 (6.9%)</td>
<td>0/29</td>
<td></td>
</tr>
<tr>
<td><strong>B-blockers</strong></td>
<td>5/29 (17.2%)</td>
<td>5/29 (17.2%)</td>
<td>1/29 (3.4%)</td>
<td>0/29</td>
<td></td>
</tr>
<tr>
<td><strong>Statins</strong></td>
<td>0/29 (0%)</td>
<td>0/29 (0%)</td>
<td>0/29 (0%)</td>
<td>6/29 (20.7%)</td>
<td></td>
</tr>
<tr>
<td><strong>Ca-channels blockers</strong></td>
<td>2/29 (6.9%)</td>
<td>2/29 (6.9%)</td>
<td>1/29 (3.4%)</td>
<td>0/29</td>
<td></td>
</tr>
<tr>
<td><strong>Diuretics</strong></td>
<td>3/29 (10.3%)</td>
<td>2/29 (6.9%)</td>
<td>1/29 (3.4%)</td>
<td>1/29 (3.4%)</td>
<td></td>
</tr>
<tr>
<td><strong>Others (Gliptins)</strong></td>
<td>1/29 (3.4%)</td>
<td>1/29 (3.4%)</td>
<td>0/29 (0%)</td>
<td>0/29</td>
<td></td>
</tr>
</tbody>
</table>

Values are mean ± SE. Letters indicate statistically significant difference from: (a) healthy, (b) D0, (c) D14; p<0.05. BMI, body mass index. OSAS, obstructive sleep apnea syndrome. LDL, low density lipoprotein. HDL, high density lipoprotein. TG, triglycerides. ACEI, Angiotensin-converting-enzyme inhibitors.

Osto E et al. Circulation 2015
HDL properties in Patients

HDL properties improved 12 weeks after RYGB to the level of healthy subjects, although the patients were still obese. Instead, HDL properties were impaired in BMI-matched patients.

degree of weight and BMI loss induced by surgery 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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F Tona, S iliceto
Thank you for your attention!
Taste domains

Sensory
Detection or Discrimination
("What is it?")

Reward
Hedonism
("How much do I like it?")

Physiology
post-ingestive effects,
CTA
Bariatric surgery reverses end organ damage Mingrone et al Diabetes Care 2011