Changes in Incretin Levels After Bariatric Surgery

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Metabolic Effects of Weight Loss and Bariatric Surgery

• Glucose Homeostasis

• Lipid Homeostasis

• Cardiovascular risk reduction
Rates of Remission of Diabetes

Adjustable Gastric Banding
48% (Slow)

Roux-en-Y Gastric Bypass
84% (Immediate)

Biliopancreatic Diversion
>95% (Immediate)

Buchwald H. JAMA, 2004
Bariatric Surgery and DM; it works EARLY

- Rubino 2004
- Pories 1998

- Many bariatric surgeons have recognized that DM improves immediately after surgery, before any significant weight loss has occurred.
- Seen in diverting procedures, not often in purely restrictive procedures
Potential Mechanisms of these Effects

• Gastric Volume Restriction
• Increased Gastric Emptying
• Central nervous system (CNS) control of energy balance
• Energy expenditure
• Gut Hormones
Horowitz M, et al.
Measurement of gastric emptying after gastric bypass surgery using radionuclides.

*Brit J Surg. 1982*

« No correlation between weight loss and gastric emptying, stoma or pouch size »
Stomach preservation vs Total gastric bypass

Rubino et al. Endocrinology 2005
Stomach preservation vs Total gastric bypass

Food Intake

- **GBP**
- **SHAM**
- **EJ**
Food Intake: Obese vs Lean rats

**Obese rats**

Rubino et al. Endocrinology 2005

**Lean rats**

Rubino et al. Endocrinology 2005
Weight gain: Obese vs Lean rats

Obese rats

P<0.001

Lean rats

P= NS

Box-and-whisker
The Role of Gut Hormones
(and others)

- Leptin
- Ghrelin
- Glucose-Dependent Insulinotropic Polypeptide (GIP)
- Glucagon-like peptide-1
- Cholecystokinin (CCK)
- Peptide-YY
- Pancreatic polypeptide (PP)
- Bile Acids
- Insulin
Leptin

• Consistent with the large reduction in fat mass, plasma leptin levels do drop after RYGB, VSG, and AGB

• reduction in plasma leptin levels after RYGB and VSG exceeds the reduction observed in weight-matched control subjects
Leptin

- VSG had no advantage over caloric restriction to improve leptin sensitivity
- Furthermore, VSG is effective in rodent models of obesity where leptin sensitivity cannot be increased due to a lack of functional leptin receptors.

- Conclusion: although RYGB and VSG reduce the normal responses to negative energy balance, they do not rely primarily on increased leptin sensitivity to do so.
Ghrelin

- VSG involves the removal of ghrelin-producing mucosa
- Circulating ghrelin levels are reduced after VSG in humans and in rodents
- Increased after band surgery in humans and rodents
- RYGB, the literature is fraught with controversy and conflicting results
Ghrelin

Ghrelin

• To assess whether ghrelin plays a role in the metabolic
  benefits observed after VSG directly

• VSG on animals that lack a functional copy of the ghrelin
  gene and compared them with wild-type controls.

• Effect of the surgery on body weight and glucose
  homeostasis in these animals was unaltered

Glucose-Dependent Insulinotropic Polypeptide (GIP)

- enhances glucose-dependent insulin secretion and promotes beta cell proliferation
- Higher levels of basal GIP as well as an increased early phase postprandial GIP response were seen in obese subjects compared to lean
- exogenous administration of GIP raised glucose levels in type 2 diabetic patients in both early and late postprandial phases

<table>
<thead>
<tr>
<th>Author/year</th>
<th>Type of study</th>
<th>Subjects</th>
<th>Preop BMI</th>
<th>% weight loss</th>
<th>RVU time</th>
<th>Change in hormone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laferrère et al. 2007 [30]</td>
<td>Prospective controlled</td>
<td>7 nonobese</td>
<td>43.6 ± 4.8</td>
<td>37.1 ± 11.4</td>
<td>NA</td>
<td>1 mo</td>
</tr>
<tr>
<td>Laferrère et al. 2008 [49]</td>
<td>Prospective controlled</td>
<td>10 T2D RVGB</td>
<td>43.5 ± 6.3</td>
<td>43.9 ± 3.4</td>
<td>NA</td>
<td>1 mo</td>
</tr>
<tr>
<td>Rabino et al. 2004 [60]</td>
<td>Prospective uncontrolled</td>
<td>10 (9 F, 1 M) RVGB</td>
<td>65.2</td>
<td>NA</td>
<td>3 wk</td>
<td></td>
</tr>
<tr>
<td>Clementi et al. 2004 [61]</td>
<td>Prospective uncontrolled</td>
<td>20 obese (12 F) with T2D</td>
<td>52.7 ± 8.8</td>
<td>NA</td>
<td>24 and 12 wk postop</td>
<td>Decrease in fasting GIP at 6 and 12 wk. Decrease in fasting GIP at 6 and 12 wk.</td>
</tr>
<tr>
<td>Whilton et al. 2007 [71]</td>
<td>Prospective uncontrolled</td>
<td>10 (9 F, 1 M) RVGB</td>
<td>50 ± 6</td>
<td>NA</td>
<td>6 mo</td>
<td>No change in GIP postop (fasting).</td>
</tr>
<tr>
<td>Kaszyn et al. 2010 [73]</td>
<td>Prospective uncontrolled</td>
<td>16 (7 females) with T2D</td>
<td>47 ± 9</td>
<td>10%</td>
<td>4 wk</td>
<td>No change in fasting or PP GIP in both groups.</td>
</tr>
<tr>
<td>Kern et al. 2007 [74]</td>
<td>Cross-sectional controlled</td>
<td>RVGB</td>
<td>35.6 ± 3.4</td>
<td>26.6 ± 2.9</td>
<td>NA</td>
<td>Blunted PP GIP peak after RVGB</td>
</tr>
<tr>
<td>Kern et al. 2007 [75]</td>
<td>Cross-sectional controlled</td>
<td>7 RVGB</td>
<td>33.3 ± 1.9</td>
<td>26.6 ± 2.9</td>
<td>3.5</td>
<td>Blunted PP GIP peak after RVGB</td>
</tr>
</tbody>
</table>


Glucagon-like peptide-1

- release of insulin through actions on GLP-1 receptors expressed on β-cells
- In addition to its incretin effect, GLP-1 inhibits gastric acid secretion, gastric emptying, glucagon secretion, hepatic glucose production, and food intake through actions that involve the coordinated effects of GLP-1 receptors expressed in the periphery and CNS.
- Other than the established role of GLP-1 in the incretin effect, the fundamental role of GLP-1 release on food intake, body weight, insulin sensitivity, taste preference, and other effects of VSG and RYGB remain to be tested
Glucagon-like peptide-1

Chambers AP et al. Weight-independent changes in blood glucose homeostasis after gastric bypass or vertical sleeve gastrectomy in rats. Gastroenterology 141:950, 2011 (48),
Cholecystokinin (CCK)

- satiety hormone responsible for modulating hunger in response to meal onset
- Duodenum and jejunum
- suppresses food intake by reducing meal size through its action on CCK receptors on vagal afferents
Cholecystokinin (CCK)

- initial studies demonstrate no change to plasma CCK after either RYGB or AGB
- RYGB is effective in CCK-1-deficient, Otsuka Long-Evans Tokushima Fatty rats

Peptide-YY

- released postprandially from the distal gastrointestinal tract, acts within the arcuate nucleus to inhibit the release of NPY. Intravenous PYY3–36 infusions into humans and intraperitoneal injections into rodents induce satiety and reduce food intake.

- RYGB and other procedures are associated with exaggerated postprandial PYY secretion. This effect increases over time.

- reported to be integral to RYGB-induced weight loss, because short-term weight loss is attenuated in mice that do not make PYY.

- weight regain after RYGB in humans has been linked to low plasma PYY levels.
Bypass Procedures

Bariatric Surgery Effects on Hormones

GLP-1

PYY

Ileal transposition (interposition)

- 10 cm distal transection
- Vascularly intact
- Innervated
- Isoperistaltic
Plasma PYY (1-36)

Time (minutes) 0 15 30 45 60 90 120 180

Plasma PYY (pmol/l) 0 100 200 300 400 500

- Sham
Plasma PYY (1-36)

Time (minutes)

Plasma PYY (pmol/l)

- Sham
- Ileal transposition

* p<0.05

Strader et al., AJP, 2005
Plasma GLP-1

Time (minutes)

Plasma GLP-1 (pmol/l)

Sham
Plasma GLP-1

*\( p < 0.05 \)
Patriti: Results

• IT improved Glucose Tolerance, Insulin Sensitivity and Acute Insulin Response without any changes in body weight or diet
  – Inc sustained response by GLP1
  – Inc gene expression in transposed ileum
  – Immunohistochemical

  – No changes in GIP
Fig 2. Glucose tolerance in type 2 diabetic rats: The AUCs of the blood glucose curves were determined during the postoperative OGGTs in IT rats, sham-operated and control diabetic rats. IT resulted in a markedly better glucose tolerance compared with both sham-operated and control rats. ***P < .001.
Results
Bile Acids

• Activate nuclear transcription factors that regulate genes involved in glucose metabolism in liver and brain

• Activate TGR5, gut receptor that regulates GLP-1 secretion

• Increased blood levels after VSG and RGB
**TABLE 1.** Characteristics and PYY, Insulin, GLP-1, Leptin, Ghrelin, and Pancreatic Polypeptide During the Single 420-kcal Meal Study in Lean, Obese, Bypass, and Banding Subjects

<table>
<thead>
<tr>
<th>Single Meal Study</th>
<th>Control Subjects</th>
<th>Surgical Patients</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lean</td>
<td>Obese</td>
<td>Bypass</td>
<td>Banding</td>
</tr>
<tr>
<td>N (females)</td>
<td>15 (13)</td>
<td>12 (9)</td>
<td>6 (6)</td>
<td>6 (6)</td>
</tr>
<tr>
<td>Age (yr) [mean (SD)]</td>
<td>34.8 (8.90)</td>
<td>37.9 (5.54)</td>
<td>39.3 (3.6)</td>
<td>40.3 (10.7)</td>
</tr>
<tr>
<td>Baseline BMI (kg/m²) [mean (SD)]</td>
<td>23.8 (3.03)</td>
<td>47.1 (5.76)</td>
<td>49.8 (10.8)</td>
<td>46.1 (4.59)</td>
</tr>
<tr>
<td>Months postoperation [mean (SD)]</td>
<td></td>
<td></td>
<td>11.2 (6.5)</td>
<td>19.2 (3.3)</td>
</tr>
<tr>
<td>Postoperation BMI (kg/m²) [mean (SD)]</td>
<td></td>
<td></td>
<td>36.8 (7.56)</td>
<td>36.3 (4.15)</td>
</tr>
<tr>
<td>Fasting PYY (pmol/L) [mean (SD)]</td>
<td>15.4 (8.3)</td>
<td>13.8 (7.1)</td>
<td>18.5 (5.2)</td>
<td>12.9 (6.1)</td>
</tr>
<tr>
<td>90 min PYY (pmol/L) [mean (SD)]</td>
<td>23.7 (9.5)</td>
<td>16.0 (8.1)</td>
<td>40.4 (7.8)</td>
<td>18.0 (8.9)</td>
</tr>
<tr>
<td>PYY AUC (pmol/L per min) [mean (SD)]</td>
<td>1308 (552)</td>
<td>633 (267)</td>
<td>3082 (670)</td>
<td>913 (393)</td>
</tr>
<tr>
<td>HOMA (IR)</td>
<td>1.36 (1.12)</td>
<td>4.22 (1.65)</td>
<td>1.94 (1.16)</td>
<td>1.46 (1.05)</td>
</tr>
<tr>
<td>15 min insulin (mU/L) [mean (SD)]</td>
<td>9.15 (7.06)</td>
<td>18.4 (9.64)</td>
<td>30.3 (15.2)</td>
<td>11.6 (11.9)</td>
</tr>
<tr>
<td>Δ insulin 15 min (mU/L) [mean (SD)]</td>
<td>3.3 (6.9)</td>
<td>2.6 (9.8)</td>
<td>22.3 (15.9)</td>
<td>3.8 (7.3)</td>
</tr>
<tr>
<td>30 min GLP-1 (pmol/L) [mean (SD)]</td>
<td>20.2 (9.0)</td>
<td>13.5 (6.9)</td>
<td>47.4 (11.3)</td>
<td>14.0 (6.2)</td>
</tr>
<tr>
<td>Fasting leptin (ng/mL) [mean (SD)]</td>
<td>6.3 (3.3)</td>
<td>16.5 (4.3)</td>
<td>10.2 (2.2)</td>
<td>11.1 (2.7)</td>
</tr>
<tr>
<td>Fasting ghrelin (pmol/L) [mean (SD)]</td>
<td>700.6 (60.7)</td>
<td>446.1 (117.6)</td>
<td>430.4 (53.2)</td>
<td>491.3 (120.8)</td>
</tr>
<tr>
<td>30 min PP [mean (SD)]</td>
<td>44.5 (24.2)</td>
<td>59.1 (52.1)</td>
<td>43.2 (44.4)</td>
<td>63.0 (44.1)</td>
</tr>
</tbody>
</table>

NS indicates not significant.
<table>
<thead>
<tr>
<th></th>
<th>RYGB</th>
<th>AGB</th>
<th>VSG</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lipid homeostasis</strong></td>
<td>Elevated HDL</td>
<td>Elevated HDL</td>
<td>Elevated HDL</td>
</tr>
<tr>
<td></td>
<td>Reduced triglycerides</td>
<td>Reduction in triglycerides not as</td>
<td>Reduction in triglycerides</td>
</tr>
<tr>
<td></td>
<td>Reduced total cholesterol, LDL</td>
<td>dramatic as RYG or VSG</td>
<td></td>
</tr>
<tr>
<td><strong>Glucose homeostasis</strong></td>
<td>Improved fasting blood glucose and</td>
<td>Improvements are slower and not</td>
<td>Improved fasting blood glucose and</td>
</tr>
<tr>
<td></td>
<td>insulin sensitivity, prior to weight loss</td>
<td>as dramatic as after VSG or RYG</td>
<td>insulin sensitivity, prior to weight loss</td>
</tr>
<tr>
<td><strong>Role of gastric restriction</strong></td>
<td>Has not yet been directly tested</td>
<td>Failure of band leads to less</td>
<td>Gastric restriction is not the critical</td>
</tr>
<tr>
<td></td>
<td></td>
<td>gastric restriction and less</td>
<td>factor preventing hyperphagia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>weight loss</td>
<td></td>
</tr>
<tr>
<td><strong>Gastric emptying</strong></td>
<td>Few published studies</td>
<td>No overall change in gastric</td>
<td>Most papers show increase</td>
</tr>
<tr>
<td></td>
<td></td>
<td>emptying rate; Emptying rate of</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>proximal pouch created by band</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>is enhanced</td>
<td></td>
</tr>
<tr>
<td><strong>Energy expenditure</strong></td>
<td>Controversial</td>
<td>Not reported</td>
<td>Unchanged, but only reported in one study</td>
</tr>
<tr>
<td><strong>Leptin</strong></td>
<td>Circulating leptin levels lower than</td>
<td>Plasma leptin reduced, as</td>
<td>Circulating leptin levels lower than</td>
</tr>
<tr>
<td></td>
<td>expected for body weight; Changes to</td>
<td>expected for body weight; Changes to</td>
<td>expected for body weight; Body weight</td>
</tr>
<tr>
<td></td>
<td>leptin sensitivity not tested</td>
<td>leptin sensitivity not tested</td>
<td>changes not driven by changes to leptin</td>
</tr>
<tr>
<td><strong>Ghrelin</strong></td>
<td>Reduced total ghrelin;</td>
<td>Increased circulating ghrelin</td>
<td>Reduced total ghrelin;</td>
</tr>
<tr>
<td></td>
<td>Controversial, but no change in</td>
<td></td>
<td>Controversial, but no change in</td>
</tr>
<tr>
<td></td>
<td>acylghrelin levels</td>
<td></td>
<td>acylghrelin levels</td>
</tr>
<tr>
<td><strong>CCK</strong></td>
<td>No change</td>
<td>No change</td>
<td>Not measured</td>
</tr>
<tr>
<td><strong>GLP-1</strong></td>
<td>Weight loss-independent postprandial</td>
<td>Increased circulating GLP-1 but</td>
<td>Weight loss-independent increase</td>
</tr>
<tr>
<td></td>
<td>increase</td>
<td>much less than RYG or VSG</td>
<td>comparable to RYG</td>
</tr>
<tr>
<td><strong>PYY</strong></td>
<td>Increased postprandial PYY levels; Reduced</td>
<td>No change</td>
<td>Increased postprandial PYY levels,</td>
</tr>
<tr>
<td></td>
<td>body weight loss in PYY knock-out mice</td>
<td></td>
<td>comparable to levels after RYG</td>
</tr>
<tr>
<td><strong>Bile acids</strong></td>
<td>Increased plasma bile acids</td>
<td>Not reported</td>
<td>Increased plasma bile acids</td>
</tr>
<tr>
<td><strong>Diet Change</strong></td>
<td>Decreased fat intake, more fruits</td>
<td>Decreased bread intake and</td>
<td>Decreased fat intake, similar to</td>
</tr>
<tr>
<td></td>
<td>and vegetables</td>
<td>increase in caloric liquids; Greater</td>
<td>RYG</td>
</tr>
<tr>
<td><strong>Food Intolerance</strong></td>
<td>Some dumping syndrome, usually</td>
<td>More persistent and problematic</td>
<td>Little or none</td>
</tr>
<tr>
<td></td>
<td>well tolerated</td>
<td>than RYG</td>
<td></td>
</tr>
</tbody>
</table>