Grand Rounds
St Charles Medical Center

Diabetes
May Be a Surgical Disease
Stephen Archer, MD
Metabolic Surgeon
September 14, 2012
Grand Rounds

Another Bariatric Talk?

- 9 million adults with severe morbid obesity
- >1% undergo bariatric surgery
- 1/10 eligible adults have had bariatric surgery discussion with their doctor
- Most primary care MD's believe lifestyle changes are more effective to lose weight and much more than bariatric surgery
- 3.8% primary care MD's have heard of consensus statement on Gastrointestinal Surgery for Severe Obesity published by NIH in 1991
- All statement above supported by peer review publication within last five years

Why?
- NASMBS (Now known as the American Society for Bariatric Surgery (ASBMS), The name change comes nearly 25 years after the Society was founded. The Society has mainly

Gene-Environment Interactions

Disproportional Increase in Severe Obesity

More than 1,500,000 U.S. adults now have a BMI >50
What is a Sleeve Gastrectomy?

Questions?

Does operating on the stomach improve diabetes?

Is surgery more effective than alternatives?

Is so, how?

What about weight loss?

Why?

After Gastric Bypass, Patients Are Discharged Home on Few or No Diabetes Medications

Why?
How Does Gastric Bypass Induce Remission of Diabetes?

- Weight loss via restriction—perhaps 1/2 of the effect, if gastric banding is an indication
- Metabolic effect
  - Incretin-gut hormones that stimulate insulin secretion or insulin sensitivity postprandially
  - Exendrin 4
  - Heloderma suspectum

The incretin effect

- Secreted in the ileum, L cells
- Half-life 3-7 minutes
- Levels peak 20 minutes after a meal
- Inactivated by dipeptidyl peptidase IV
- Effect on insulin secretion first described in 1985 by Creuzfeldt and Ebert

Glucagon-Like Peptide-1

- Secreted in the ileum, L cells
  - Half-life 3-7 minutes
  - Levels peak 20 minutes after a meal
  - Inactivated by dipeptidyl peptidase IV
  - Effect on insulin secretion first described in 1985 by Creuzfeldt and Ebert

How Does Gastric Bypass Induce Remission of Diabetes?

- Weight loss via restriction—perhaps 1/2 of the effect, if gastric banding is an indication
- Metabolic effect
  - Incretin-gut hormones that stimulate insulin secretion or insulin sensitivity postprandially
  - Exendrin 4
  - Heloderma suspectum

The incretin effect

- Secreted in the ileum, L cells
- Half-life 3-7 minutes
- Levels peak 20 minutes after a meal
- Inactivated by dipeptidyl peptidase IV
- Effect on insulin secretion first described in 1985 by Creuzfeldt and Ebert
GLP-1 Physiology

GLP-1 in Non-Diabetic, Non-Obese Individuals

- Meal
- Slowed Gastric Emptying
- Stomach Volume
- Duodenal Gush
- Hyperosmotic fluid in ileum (↑Glc)

Brener, Gastroenterology 85:76:1983

GLP-1 in Normal Obese, T2D Individuals

- Meal
- ↑Insulin
- Slowed Gastric Emptying
- Duodenal Gush
- Hyperosmotic fluid in ileum (↑Glc)

- Slowed Intestinal Transit

↑Insulin
Rapid transit allows glucose to reach hindgut

Obes Surg 8. 253.1998

GLP-1 in Normal Obese, T2D Individuals

- Meal
- ↑Insulin
- Slowed Gastric Emptying
- Duodenal Gush
- Hyperosmotic fluid in ileum (↑Glc)

↑Insulin
Rapid transit allows glucose to reach hindgut

Obes Surg 8. 253.1998

GLP-1

- Obese, Type 2 Diabetic
  - No rise in GLP-1 after oral glucose load (meal)
  - Reason unknown
  - Related to failure of antro-duodenal-pyloric control of gastric emptying
  - Gut 38.916, 1996

- Obese, Type 2 Diabetic After Gastric Bypass
  - GLP-1 levels rise to normal within days

Gastric emptying after VSG and RYGB

- Stomach
- Ultrasound (USG)
- RYGB

Mechanisms of Diabetes Improvement

- Gastric Banding
- Gastric Bypass
- Weight Loss
- Control of Diabetes
- Immediate effect
- Gradual effect
Minimize Surgery and Harness GLP-1 Effects:
Duodenal Sleeve

The impermeable fluoropolymer sleeve is placed via an endoscope and fastened with a barbed metal anchor at the duodenal entrance. The 16 patients in the study had a mean baseline BMI of 38 and a hemoglobin A1c of 9%. After only one week, the daily average glucose level declined 58.4 mg/dL (SD 54.5 mg/dL) among 11 patients receiving the bypass sleeve, compared with an increase of 1.1 mg/dL (SD 45.7 mg/dL) in five sham-treated patients (P < 0.05), according to interim results.
How Do Gastric Bypass and sleeve gastrectomy Induce weight loss?

- Let's start with a diet
- Rats: we can control what they eat
- After a diet their weight finds its way back to baseline

Why Diets usually fail

Resting energy expenditure (REE) and total energy expenditure (TEE) both drop
Obesity

**Historical view**
- Lifestyle choice
- Characterological flaw (willpower, psychology)

**Current perspective**
- Complex physiology
- Epidemic from changes in modern environment
- Widely recognized as a disease
- Huge burden of associated illness -- a cause of more than 50% of all medical disorders (incl. 12 types of cancer)
- Devastating effect on quality and efficacy of life

Is ghrelin lower after RYGB?

<table>
<thead>
<tr>
<th>GI Endocrine Responses to RYGB</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GLP-1</strong></td>
</tr>
<tr>
<td><img src="image1" alt="Graphs" /></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RYGB Selectively Reduces Body Fat</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image4" alt="Graph" /></td>
</tr>
</tbody>
</table>

**Differential Effects of GI Manipulations**

<table>
<thead>
<tr>
<th>Weight</th>
<th>Food intake</th>
<th>Energy Expended</th>
<th>Insulin sensitivity</th>
<th>Glucose tolerance</th>
<th>Insulin secretion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastric Banding</strong></td>
<td>+++</td>
<td>+++</td>
<td>--</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Endoluminal Sleeve</strong></td>
<td>++</td>
<td>++</td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
</tr>
<tr>
<td><strong>Intestinal Interposition</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gastric Bypass</strong></td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>++++</td>
<td>++++</td>
</tr>
<tr>
<td><strong>BPD/DS</strong></td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>++++</td>
<td>++++</td>
</tr>
</tbody>
</table>

**Endocrine Effects of GI Manipulations**

<table>
<thead>
<tr>
<th></th>
<th>Glucoin</th>
<th>GLP-1</th>
<th>PYY</th>
<th>GIP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastric Banding</strong></td>
<td>↑</td>
<td>⊗</td>
<td>⊗</td>
<td>⊗</td>
</tr>
<tr>
<td><strong>Sleeve Gastrectomy</strong></td>
<td>⊗</td>
<td>⊗</td>
<td>↑*</td>
<td>↑*</td>
</tr>
<tr>
<td><strong>Ileal Interposition</strong></td>
<td>⊗</td>
<td>↑*</td>
<td>↑*</td>
<td>↓</td>
</tr>
<tr>
<td><strong>Endoluminal Bileterer</strong></td>
<td>⊗</td>
<td>↑*</td>
<td>↑*</td>
<td>⊗</td>
</tr>
<tr>
<td><strong>Gastro Bypass</strong></td>
<td>Variable</td>
<td>↑*</td>
<td>↑*</td>
<td>⊗</td>
</tr>
<tr>
<td><strong>BPD/DS</strong></td>
<td>Variable</td>
<td>↑*</td>
<td>↑*</td>
<td>↑*</td>
</tr>
</tbody>
</table>

*Post prandial*
RYGB Mimics the Overfed State

Surgery Decreases Long-term Mortality

Utah Bariatric Surgery Study
- 15000 gastric bypass patients and matched controls
- 7.1 year mean follow-up
- Gastric bypass group exhibited overall 40% reduction in mortality
- Specific-cause mortality after gastric bypass
  - 60% reduction in mortality from CAD
  - 92% reduction in mortality from type 2 diabetes
  - 60% reduction in mortality from cancer

What Seems Clear
- Surgery alters the normal physiology of energy balance and metabolic regulation
- Surgery enhances regulatory signaling from the gut to the rest of the body
- Different procedures employ different mechanisms of action
  - Therefore they have different clinical characteristics
- RYGB influences glucose homeostasis through both weight loss-dependent and weight loss-independent mechanisms
- The GI tract is a critical regulator of energy balance and metabolic function
- Appropriate manipulations of the GI tract are likely to provide major advances in the effective treatment of obesity and its complications

What is Less Clear
- The degree to which the observed hormonal changes mediate physiological responses to surgery
- The role of the autonomic and enteric nervous systems in the response to surgery
- The primary signals that regulate altered gut signaling after surgery
  - e.g., nutrients, endogenous secreted hormones, microRNA
- The degree to which gut manipulation causes slowing, or even reversal of pancreatic β-cell dysfunction
- How best to reproduce the effects of surgery with devices, medications and food-based therapies

Vertical Sleeve Gastrectomy (VSG)
Weight Loss after RYGB is Widely and Normally Distributed

Number of Patients

% Excess Body Weight Loss at 1 year

n=652

Vertical Sleeve Gastrectomy (VSG)