Metabolic Surgery: Endocrine Mechanisms of Diabetes Remission After “Bariatric” Operations

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I am P.I. on the COSMID trial (Comparison of Surgery vs. Medicines for Indian Diabetes), funded by Johnson & Johnson
Some Clinically Used Bariatric Operations

**Adjustable Gastric Banding (LAGB)**

**Roux-en-Y Gastric Bypass (RYGB)**

**Bilio-Pancreatic Diversion (BPD)**
Roux-en-Y Gastric Bypass (RYGB)
Swedish Obese Subjects Study

Total Body Weight Loss (%)

Years of Follow Up

Usual Care
Banding
Gastroplasty
Gastric Bypass

Bariatric Operative Mortality

- Pure Restrictive Procedures: <0.1%
- Lap Gastric Bypass: 0.2%
- BPD or DS: 1.1%

Most perioperative mortality from PE or sepsis
<table>
<thead>
<tr>
<th>Study</th>
<th>Procedure</th>
<th>F/U</th>
<th>Mortality Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>MacDonald, 1997</td>
<td>RYGB</td>
<td>9 yr</td>
<td>88%</td>
</tr>
<tr>
<td>Flum, 2004</td>
<td>RYGB</td>
<td>4.4 yr</td>
<td>33%</td>
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<tr>
<td>Christou, 2004</td>
<td>RYGB</td>
<td>5 yr</td>
<td>89%</td>
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<tr>
<td>Sowemimo, 2007</td>
<td>RYGB</td>
<td>4.4 yr</td>
<td>63%</td>
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<tr>
<td>Dixon, 2007</td>
<td>LAGB</td>
<td>12 yr</td>
<td>72%</td>
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<tr>
<td>Adams, 2007</td>
<td>RYGB</td>
<td>8.4 yr</td>
<td>40%</td>
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<tr>
<td>Sjostrom, 2007</td>
<td>VBG/other</td>
<td>14 yr</td>
<td>31%</td>
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<tr>
<td>Perry, 2008</td>
<td>RYGB/LAGB</td>
<td>2 yr</td>
<td>48%</td>
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</tbody>
</table>
Cost per QALY

- **Bariatric surgery**: $3,200 – $6,300
- **Renal Dialysis**: $50,000 (accepted societal std)
# Bariatric Surgeries in the USA

How does gastric bypass cause type 2 diabetes remission?
Gastric Bypass Reverses Diabetes

- **80-85% full remission** of type 2 DM after RYGB
  - Buchwald meta-analysis 22,094 patients
  - Schauer, et al. 1,160 patients
  - Whitgrove, et al. 1,029 patients
  - Pories, et al. 608 patients
  - Buchwald meta-analysis 2 135,246 patients
  - Many others
How does it work?
Swedish Obese Subjects Study

Total Body Weight Loss (%)

Gastric Bypass
Gastroplasty
Gastric Banding
Medical Management

No. Examined

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<td>Vertical-banded gastroplasty</td>
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<tr>
<td>Gastric bypass</td>
<td>265</td>
<td>245</td>
<td>245</td>
<td>211</td>
<td>209</td>
<td>166</td>
<td>92</td>
<td>58</td>
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Insulin Sensitivity After RYGB

- ↑ hepatic, muscle, and adipose insulin sensitivity
- ↑ HMW adiponectin, ↓ apelin
- ↓ inflammatory cytokines, ER stress, YKL-40
- ↓ hepatic steatosis-inducing factor CIDE C
- ↓ intramuscular & hepatic lipids & FACoA
- ↑ muscle insulin receptor concentration
- ↑ muscle PGC1 and its target Mfn2

* All Long-Term Effects *
↑ insulin sensitivity with weight loss undoubtedly plays an important role
Rapid Improvement of Diabetes After RYGBP

Days After Surgery

Blood Glucose (mg/dl)

- 0 units insulin
- 90 units insulin

Adapted from Pories W, 1980
Rapid Resolution of Diabetes After RYGB

- Prospective study of 1160 RYGB patients
- 240 with DM on oral meds and/or insulin, 80% F/U
- 83% DM resolution

![Bar chart showing % Diabetes Resolved Upon Initial Hospital Discharge](chart.png)

Just Starvation & Weight Loss or Something Special?
Rates of Remission of Diabetes

- Adjustable Gastric Banding: 48% (Slow)
- Roux-en-Y Gastric Bypass: 84% (Immediate)
- Biliopancreatic Diversion: >95% (Immediate)
Evidence for Weight-Independent Anti-DM Effects

- Fast kinetics of diabetes resolution

- Glucose homeostasis improves more with RYGB than with equal weight loss from other means

Poor correlation between amount of weight lost and DM remission rates after RYGB
Long-Term Follow-Up of Gastric Bypass vs. Gastric Banding

C. le Roux, et al
**Trial of Gastric Banding vs. Bypass**

Inclusion:
- BMI > 35 kg/m² and type 2 diabetes

AGB  
- 10% weight loss
- 1 year

RYBG

Controlled, non-randomized, prospective study
- 50 Patients

HbA1c  
- HOMA-IR
- Insulin (test meal)
- Incretins

Francois Pattou  
(Lille, France)
Glycemic Responses to Post-op Test Meal

After **10% Weight Loss in Both Groups**

![Graph showing plasma glucose levels post-test meal for Gastric Banding and Gastric Bypass.](image)

- **Plasma Glucose**
  - Gastric Banding
  - Gastric Bypass

Time After Test Meal

F Pattou, et al
Effects on Glucose Homeostasis of Equivalent Weight Loss from RYGB vs. Diet

Type 2 diabetes patients matched for BMI, age, degree of diabetes

RYGB studied at ↓ 9.7 kg

Diet studied at ↓ 9.2 kg

Laferrère et al
JCEM 93:2479, 2008
More Improved Glucose Tolerance After RYGB Than After Equivalent Dietary Weight Loss

Laferrère et al
JCEM 93:2479, 2008
Randomized Trial for T2DM Treatment: Sleeve Gastrectomy vs. Gastric Bypass

Type 2 diabetes patients
- HbA1c > 8%
- BMI 27-35

BMI: 30
- HbA1c: 10%
- LDL, TG, age, gender

Matched

Randomization

n = 15

Sleeve Gastrectomy

n = 15

Sleeved Gastric Bypass

Lee WJ et al 2009
No Differences in Body Weight or Weight Loss at 6 mo.

Lee WJ et al, 2009

Sleeve Gastrectomy
Gastric bypass

~15% ↓ wgt @ 6 mo
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<th>Endpoint</th>
<th>Sleeve Gastrectomy</th>
<th>Gastric Bypass</th>
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</thead>
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<td>% A1c &lt;7.0</td>
<td>46.7%</td>
<td>93.3%</td>
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<tr>
<td>LDL</td>
<td>↑ 23</td>
<td>↓ 16 mg/dL</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>↓ 107</td>
<td>↓ 130 mg/dL</td>
</tr>
<tr>
<td>% at Rx Goals</td>
<td>14%</td>
<td>60%</td>
</tr>
<tr>
<td>- A1c &lt; 7%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- LDL &lt; 130</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- TG &lt; 150</td>
<td></td>
<td></td>
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</tbody>
</table>

Lee WJ et al, 2009
Weight Loss After RYBG in Obese Zucker Rats

Meirelles K, et al
Better Oral Glucose Tolerance After RYGB Than After Similar Weight Loss From Food Restriction in Rats

Plasma Glucose (mg/dl)

Sham Operated Pair-Fed Sham

RYGB

Time After Gavage (min)

Meirelles K, *et al*
Evidence for Weight-Independent Anti-DM Effects

- Fast kinetics of diabetes resolution
- Glucose homeostasis improves more with RYGB than with equal weight loss from other means
- Inconsistent correlation between amount of weight lost and DM remission rates after RYGB
Asian Indians Have Increased DM Risk at Lower BMIs Compared with Caucasians

22.3 BMI 22.3

9.1% Body Fat 21.2%

Yajnik & Yudkin
*Lancet* 363:163
Asian Indians Have Increased Diabetes Risk at Lower BMI Levels


![Graph showing diabetes incidence per 1000 person-years vs. BMI for different ethnic groups.](image)
Asian Indians Are Vulnerable to Developing Type 2 Diabetes

- High % body fat for a given body weight
- Preferential visceral fat distribution
- Genetic predisposition to:
  - $\uparrow$ insulin resistance
  - $\downarrow$ $\beta$–cell volume
  - $\downarrow$ glucose-mediated insulin secretion
# W.H.O. Definitions by BMI Level

<table>
<thead>
<tr>
<th></th>
<th>“Overweight”</th>
<th>“Obese”</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most People</td>
<td>25-29.9 kg/m²</td>
<td>≥ 30 kg/m²</td>
</tr>
<tr>
<td>Asian Indians</td>
<td>23-24.9 kg/m²</td>
<td>≥ 25 kg/m²</td>
</tr>
</tbody>
</table>
Projected Global Incidence of Type 2 DM

India: 50.8
China: 29.4
USA: 22.7
Indonesia: 13.6
Pakistan: 8.7
Bangladesh: 6.4
Brazil: 7.6
Japan: 4.8
Egypt: 4.3
Turkey: 4.3

Prospective Study of RYGB for Type 2 DM in Asian Indians With BMI < 35 kg/m$^2$

- **BMI 22–35 kg/m$^2$**
  - “Overweight” to “Obese” by Indian-specific WHO criteria

- **Type 2 DM**
  - Confirmed with Abs, C-peptide, FHx

- **Severe diabetes**
  - Mean duration: 9 years
  - 80% on insulin (the rest on oral DM meds)
  - HbA1c: 10.1%

- **Other features**
  - Dyslipidemia: 93%
  - Hypertension: 60%
Results

• **Weight Loss**
  – Mean BMI: 28.9 → 23.0 (↓ 20%)

• **Hypertension Improved**
  – Mean systolic bp: 136 → 116
  – 67% discontinued HTN meds

• **Dyslipidemia Improved**
  – Mean cholesterol: 175 → 135
  – Mean HDL: 37 → 50
  – 100% discontinued lipid meds

Shah S.....
Cummings DE, *SOARD* 2010
Gastric Bypass in Asian Indians
With DM & BMI <35 kg/m²

Fasting Blood Glucose (mg/dL)

% Off All DM Meds

Shah S.....
Cummings DE,
SOARD 2010
Gastric Bypass in Asian Indians
With DM & BMI <35 kg/m²

HbA1c (%)

0%  80%  100%  100%  100%

Months After Surgery

% Off All DM Meds

Shah S.....
Cummings DE,
SOARD 2010
UKPDS Risk Engine 10-Year Cardiovascular Risk Predictions (%)

Coronary Heart Disease

Fatal Coronary Heart Disease

Stroke

Fatal Stroke

Shah & Cummings, SOARD 2010
RYGB in Asian Indians With BMI <35

• 100% DM remission by 3 months
  – Most by 1 month
  – All persisted now to \( \geq 2.5 \) years

• Weight loss: \( \sim 1/5 \) total body wgt

• Better than expected for severe obesity
  – \( \sim 80\% \) DM remission with \( \sim 1/3 \) body wgt loss

COSMID
Randomized Controlled Trial

Comparison Of Surgery vs. Medicines for Indian Diabetes

Shah SS, Kim K, Cummings DE
Prospective Study of RYGB for Type 2 DM in Caucasians With BMI 30–35 kg/m²

- **66 Caucasian patients**
  - 100% F/U to **6 years**

- **BMI 30–35 kg/m²**
  - Mild obesity for this population

- **Type 2 DM**
  - Confirmed with Abs, C-peptide, FHx

- **Severe diabetes**
  - Mean duration: 13 years
  - 40% on insulin (the rest on oral DM meds)
  - HbA1c: 9.7% at start
Rapid & Durable Improvement in HbA1c

Cohen RV.....
Cummings DE
Rapid & Durable Improvement in Fasting Glucose

Fasting Plasma Glucose (mg/dL)

Months After Surgery
6-Year Study of RYGB for Type 2 DM in Patients With BMI 30–35 kg/m²

- T2DM Remission: 88%
- T2DM Improvement: 11%
- No Change: 1%

Cohen RV.....
Cummings DE
Resolved

Cohen RV…….
Cummings DE

Waist Circumference (cm)

Total Body Weight Loss (%)

Improved

Total Body Weight Loss (%)

Cohen RV……
Cummings DE

Months After Surgery
Evidence for Weight-Independent Beneficial Effects of RYGB on Glycemia

• No relationship at any time point between the amount of weight lost and:
  – Decrease in fasting blood glucose
  – Decrease in HbA1c
  – Improvement beta-cell responsiveness to glucose
  – Increase in estimated insulin sensitivity (HOMA)
    • Except at 5 and 6 years
Cohen RV.....
Cummings DE

Systolic Blood Pressure (mmHg)

Diastolic Blood Pressure (mmHg)

Months After Surgery
Cohen RV......
Cummings DE
10-Year Cardiovascular Risk
Before vs. After RYGB

<table>
<thead>
<tr>
<th>Cardiovascular Event</th>
<th>Pre-Surgery (n=66) Mean Risk (%) ± SD</th>
<th>Post-Surgery (n=66) Mean Risk (%) ± SD</th>
<th>Absolute Risk Reduction</th>
<th>95% Confidence Interval</th>
<th>Relative Risk Reduction</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD</td>
<td>35.3 ± 10.0</td>
<td>10.3 ± 2.6</td>
<td>25%</td>
<td>8.2–13.3</td>
<td>71%</td>
<td>0.001</td>
</tr>
<tr>
<td>Fatal CHD</td>
<td>26.2 ± 8.1</td>
<td>5.4 ± 1.9</td>
<td>21%</td>
<td>3.7–8.0</td>
<td>84%</td>
<td>0.001</td>
</tr>
<tr>
<td>Stroke</td>
<td>5.0 ± 0.4</td>
<td>2.5 ± 1.7</td>
<td>2.5%</td>
<td>1.7–6.0</td>
<td>50%</td>
<td>0.01</td>
</tr>
<tr>
<td>Fatal Stroke</td>
<td>0.7 ± 0.3</td>
<td>0.4 ± 0.2</td>
<td>0.3%</td>
<td>0.03–0.1</td>
<td>57%</td>
<td>0.009</td>
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</tbody>
</table>
Multivariate analyses of 20-year data show additional effects of surgery, beyond weight loss, to improve diabetes prevention & remission.
Preoperative BMI does not predict DM prevention or remission in SOS or any other study, even though heavier patients lose more weight.
Evidence for Weight-Independent Anti-DM Effects

- Fast kinetics of diabetes resolution
- Glucose homeostasis improves more with RYGB than with equal weight loss from other means
- Inconsistent correlation between amount of weight lost and DM remission rates after RYGB
- Some intestinal bypass operations improve diabetes with little or no weight loss
Novel Anti-Diabetic GI Procedures

- Duodenal-Jejunal Bypass
- Duodenal-Jejunal Bypass Sleeve
- Ileal Interposition
Evidence for Weight-Independent Anti-DM Effects

- Fast kinetics of diabetes resolution
- Glucose homeostasis improves more with RYGB than with equal weight loss from other means
- Inconsistent correlation between amount of weight lost and DM remission rates after RYGB
- Some intestinal bypass operations improve diabetes with little or no weight loss
- Hints from hyperinsulinemia
Hyperinsulinemia Hypoglycemia After Gastric Bypass: Too much of a good thing for islets?

Late onset: 1-9 years (typical 2-4)

Service et al. NEJM 353:249 (2005)
Evidence for Increased $\beta$-Cell Mass After Intestinal Bypass Operations

- $\beta$-cell area & neogenesis in post-RYGB patients with hyperinsulinemic hypoglycemia?  
  - J. Service; A. Goldfine; others

- PDX-1 & $\beta$-cell regeneration (BRDU) at 1, 2, 4, 12 wk after RYGB in GK rats  
  - Z. Li

- $\beta$-cell area after ileal interposition in rats  
  - A. Strader; A. Patriti

- $\beta$-cell area after DJB in GK rats  
  - T. Kieffer (by histology); W. Inabnet & J. Korner (by VMAT2 PET)
What Causes RYGB’s Weight-Independent Anti-Diabetes Effects?
Changes in Gut Hormones?
Ghrelin

Esophagus
Stomach
Pancreas
Amylin
Enterostatin
Glucagon
Insulin
PP
Duodenum
CCK
Jejunum
APO AIV
Colon
GLP1
Oxyntomodulin
PYY
Ileum
GLP1
Oxyntomodulin
PYY
Small intestine
Ghrelin

- Peptide hormone produced primarily by stomach & proximal small intestine
- Powerfully stimulates appetite and food intake in many species, including humans
Human Plasma Ghrelin Levels Rise & Fall Shortly Before & After Every Meal

Cummings, et al. Diabetes 50:1714
Plasma Ghrelin Increases After Diet-Induced Weight Loss

Cummings, et al. NEJM 346:1623
Plasma Ghrelin Responds to Chronic Changes in Body Weight

- **Ghrelin ↑ With Weight Loss**
  - Caloric restriction
  - Cancer anorexia
  - Cachexia: cardiac, renal, pulmonary, or hepatic
  - Huntington’s disease
  - Anorexia & bulimia nervosa
  - Chronic exercise

- **Ghrelin ↓ With Weight Gain**
  - Overfeeding
  - High fat or sugar diets
  - Glucocorticoids
  - Atypical anti-psychotics
  - Valproic acid
  - Rx of celiac disease
  - Rx of anorexia nervosa
Roux-en-Y Gastric Bypass

Ingested food bypasses most of the ghrelin-producing cells
Effects of Gastric Bypass on Human Ghrelin Levels

**Prospective Decrease**
- Geloneze
  Obes Surg 13:17
- Fruhbeck
  NEJM 350:308
- Lin
  Arch Surg 139:780
- Couce
  NAASO 2003
- Morinigo
  Obes Res 12:1108
- Chan
  Obesity 14:194
- Foschi
  J Invest Surg 21:77
- Fruhbeck
  Obes Surg 14:1208

**Abnormally Low**
- Cummings
  NEJM 346:1623
- Tritos
  Obes Surg 11:919
- Leonetti
  JCEM 88:4227
- Rodieux
  Obesity 16:298
- Korner
  JCEM 90:359

**No Change Despite ↓ Wgt**
- Faraj
  JCEM 88:1594
- Stoeckli
  Obes Res 12:346

**Prospective Increase**
- Holdstock
  JCEM 88:3177
- Vendrell
  Obes Res 12:962
- Liou
  Obes Surg 18:84
- Karamanakos
  Ann Surg 247:401

**Impaired Ghrelin Response**
How does gastric bypass impair the normal ghrelin response to weight loss?
Hindbrain

Vagal Efferents

Gut

Adiposity Signals

Hypothalamus

Insulin

Δ Body Weight

Δ Body Weight

NO Δ Ghrelin

McLaughlin, Cummings, et al, JCEM 89:1630
Grill, Cummings, et al, unpublished
Williams, Cummings, et al, Endocrinol 144:5184
What does ghrelin have to do with diabetes?
Lower Intestinal Hypothesis
Cummings DE & Overduin J
*J Clin Invest* 117:13

<table>
<thead>
<tr>
<th>STOMACH</th>
<th>FOOD</th>
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<tbody>
<tr>
<td>Ghrelin</td>
<td>Leptin</td>
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<tr>
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<td>GRP, NMB</td>
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<table>
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<tr>
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<tr>
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<td>* GLP-1 *</td>
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<tr>
<td>Oxyntomodulin</td>
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<tr>
<td>PYY</td>
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</tbody>
</table>

↑ insulin secretion

↓ food intake
Cummings DE
& Overduin J
J Clin Invest 117:13

Food intake is regulated by various hormones and signals from different parts of the digestive tract.

**Stomach**
- Ghrelin
- Leptin
- GRP, NMB

**Duodenum**
- CCK, GIP

**Jejunum**
- APOAIV

**Ileum**
- GLP-1
- Oxyntomodulin
- PYY

**Pancreas**
- Amylin
- Enterostatin
- Glucagon
- Insulin
- PP

**Colon**
- GLP-1
- Oxyntomodulin
- PYY

Food intake decreases with
circulating GLP-1 and PYY.
Insulin secretion increases.

↑ insulin secretion
↓ food intake
Nutrient-responsive neural relay from the duodenum to distal intestine stimulates GLP-1 secretion.

Based on P. Brubaker et al.
Roux-en-Y Gastric Bypass (RYGB)

Ingested food bypasses the duodenal site of nutrient-mediated GLP-1 stimulation.
Does gastric bypass increase GLP-1 and/or PYY levels?
Increase in Postprandial GLP-1 and PYY After RYGB

GLP-1

- OW
- BAND
- BYPASS

PYY

- Lean
- Overweight
- Band
- Bypass

Meal ↑

DPP IV ↓

Korner J, et al
JCEM 90:359

Alam ML…LaFerrère B. 2011
Diabetes Obes Metab 13:378

Korner J, et al
SOARD 3:597
↑ GLP-1 For Up To 3 Years After RYGB

Laferrère et al
unpublished
Cummings DE & Overduin J
J Clin Invest 2007

All ↑ after RYGB

**STOMACH**
- Ghrelin
- Leptin
- GRP, NMB

**PANCREAS**
- Amylin
- Enterostatin
- Glucagon
- Insulin
- PP

**DUODENUM**
- CCK

**JEJUNUM**
- APOAIV

**ILEUM**
- GLP-1
- PYY
- Oxyntomodulin

**COLON**
- GLP-1
- PYY
- Oxyntomodulin
Does elevated GLP-1 after RYGB improve glucose control?
Operations That Rapidly Reverse DM

All Expedite Nutrient Delivery to the Ileum

Roux-en-Y Gastric Bypass

Biliopancreatic Diversion

Jejuno-ileal Bypass

... and All ↑ GLP-1 Levels

GLP ↑ @ 20 yrs
Post-GI Surgery ↑ GLP-1 Can Engage Key Neural Pathways

Holst and Deacon
Diabetologia 2005
Are elevated GLP-1 levels after RYGB associated with an increased *incretin effect*?
Effects on Glucose Homeostasis of Equivalent Weight Loss from RYGB vs. Diet

Type 2 diabetes patients matched for BMI, age, degree of diabetes

RYGB
Studied at ↓ 9.7 kg

Diet
Studied at ↓ 9.2 kg

Laferrière et al
JCEM 93:2479, 2008
Incretin Effect Increases After RYGB in Patients With T2DM

Laferrière et al
JCEM 93:2479, 2008
Incretin Effect on Insulin Secretion
Remains Normal Up to One Year After RYGB

Incretin Effect on Insulin Secretion
Remains Normal Up to One Year After RYGB

No change in incretin effect from equal dietary weight loss

RYGB increases the *incretin effect*, but equal dietary weight loss does not.

Laferrère et al., JCEM 93:2479, 2008
Higher C-Peptide Response to Oral Glucose After RYGB vs. Equivalent Dietary Weight Loss

C-Peptide (ng/mL)

Time (min)

Pre-RYGB
Post-RYGB
Pre-Diet
Post-Diet

Laferrière et al., JCEM 93:2479, 2008
Prandial GLP-1 response increases immediately after RYGB, along with insulin
GLP-1 Meal Responses by 3 Days After RYGB

Type 2 Diabetes

Normal Glucose Tolerance

Jens Holst, et al
C-Peptide Responses by 3 Days After RYGB

Type 2 Diabetes

Normal Glucose Tolerance

Jens Holst, et al
↑ Glucose Tolerance by 3 Days After RYGB

Type 2 Diabetes

Normal Glucose Tolerance

Jens Holst, et al
Acute Improvement in β-Cell Function
4 Weeks After RYGB vs. Gastric Restriction

(during MMTT)

Kashyap SR…., Schauer PR. IJO 34:462 (2010)
Improved insulin secretion after RYGB is not only fast but also very durable
Prospective Study of RYGB for Type 2 DM in Caucasians With BMI 30–35 kg/m²

- 66 Caucasian patients
  - 100% F/U to 6 years

- BMI 30–35 kg/m²
  - Mild obesity for this population

- Type 2 DM
  - Confirmed with Abs, C-peptide, FHx

- Severe diabetes
  - Mean duration: 13 years
  - 40% on insulin (the rest on oral DM meds)
  - HbA1c: 9.7% at start
Rapid & Durable Improvement in HbA1c After RYGB in BMI 30-35

Hemoglobin A1c (%)

Months After Surgery

Cohen RV.....
Cummings DE
Improved β–Cell Function for Up to 6 Years After RYGB

Cohen RV.....
Cummings DE

Improvements in β-cell function were observed for up to 6 years after RYGB surgery. The graphs illustrate the changes in fasting and post-meal glucose (mg/dL) and C-peptide (ng/mL) levels. Post-RYGB, there was a significant reduction in glucose levels and an increase in C-peptide levels compared to before surgery.
How much of the effects of RYGB on glucose homeostasis results from GLP-1?
GLP-1 After RYGB

• Released in correct location to engage neural (e.g., vagal) pathways to improve glucose homeostasis

• Associated with increased incretin effect

• Occurs immediately, lasts for years
Ileal Interposition

10-cm distal transection
Vascularly intact
Innervated
Isoperistaltic
Ileal Interposition

- No gastric restriction or malabsorption
- ↑ GLP-1 & PYY
- Improved glucose homeostasis
  - Beyond expected for degree of weight loss
  - ↑ Glucose-stimulated insulin secretion (GLP-1 dep)
  - ↑ β-cell mass in rats
  - Delays diabetes onset by 4 mo in rat T2DM model
Intestinal Bypass Operations That Increase Postprandial GLP-1 and Insulin Responses

- **Gastric Bypass**
  - e.g., LaFerrere, LeRoux, Korner, Holst, Schauer, Mingrone, Miller, Morinigo, Peterli, Cummings

- **Biliopancreatic Diversion**
  - e.g., Briatore, Mingrone, Ferrannini

- **Ileal Interposition**
  - e.g., Strader, Patriti, DePaula

- **Duodenal-Jejunal Bypass**
  - e.g., Ramos

...but not seen with gastric banding or dietary weight loss
What about GIP?
Cummings DE & Overduin J
J Clin Invest 117:13

STOMACH
- Ghrelin
- Leptin
- GRP, NMB

DUODENUM
- CCK, GIP

JEJUNUM
- APOAIV

ILEUM
- GLP-1
- Oxyntomodulin
- PYY

insulin secretion
↑

FOOD

PANCREAS
- Amylin
- Enterostatin
- Glucagon
- Insulin
- PP

COLON
- GLP-1
- Oxyntomodulin
- PYY

↓

food intake

↑
Cummings DE & Overduin J
J Clin Invest 117:13

**STOMACH**
- Ghrelin
- Leptin
- GRP, NMB

**DUODENUM**
- CCK, GIP

**JEJUNUM**
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- GLP-1
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**PANCREAS**
- Amylin
- Enterostatin
- Glucagon
- Insulin
- PP

**COLON**
- GLP-1
- Oxyntomodulin
- PYY

**FOOD**
- ↑ insulin secretion
- ↓ food intake
Abolished Postprandial GIP Response to Oral Glucose in GK Rats With Duodenal Bypass Sleeve

Minutes After Oral Glucose Load

<table>
<thead>
<tr>
<th></th>
<th>Complete</th>
<th>Fenestrated</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleeve</td>
<td></td>
<td></td>
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</tbody>
</table>

Rubino F
Sustained Elevation of GIP in Response to Oral Glucose for Up to 1 Year After RYGB

No Change in GIP Levels After RYGB in Type 2 DM

Jens Holst, et al

Type 2 Diabetes

Normal Glucose Tolerance

Total GIP (pM)

Time (min)
GIP seems unlikely to be a critical participant in the anti-diabetes effects of RYGB.
A Simple Model

LAGB

Time

↑ GLP-1
↑ insulin secretion
↓ body weight
↑ insulin sensitivity

RYGB

↓ body weight
↑ insulin
Does this explain everything?

<table>
<thead>
<tr>
<th>ILEUM</th>
<th>COLON</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GLP-1</strong>&lt;br&gt; Oxyntomodulin&lt;br&gt; PYY</td>
<td><strong>GLP-1</strong>&lt;br&gt; Oxyntomodulin&lt;br&gt; PYY</td>
</tr>
</tbody>
</table>

- FOOD
- ▲ insulin secretion
- ▼ food intake
NO.

Acute insulin response to \textit{I.V.} glucose in IVGTT starting very early after RYGBP (but not with similar weight loss from LAGB)

Elevated Postprandial GLP-1

Sleeve Gastrectomy

As per R. Seeley, et al
Effects of GI Surgery on Insulin Sensitivity
Insulin Sensitivity by Hyperinsulinemic Clamp in Patients with Type 2 Diabetes

* Similar weight loss between groups *

Kashyap SR,...Schauer PR IJO 34:462 (2010)
Hyperinsulinemic Clamp Studies

*Early* After GI Surgery

- **Biliopancreatic Diversion**
  - Ferrannini & Mingrone 2005 & 2006: Fast $\uparrow$ Si is not explained by weight loss, whereas slower $\uparrow$ insulin sensitivity after RYGB is explained by weight loss. *No DM in RYGB groups*

- **Gastric Bypass**
  - Campos 2009: No $\Delta$ Si at 2 weeks c/w caloric restriction. *No DM*
  - Geloneze 2010: No $\Delta$ Si at 1 month. *Mostly No DM*

  - Kashyap & Schauer 2010: $\uparrow$ Si at 1 & 4 weeks. *All DM*
  - (Cummings & Flum 2011: $\uparrow$ Si at 2 weeks?)
Upper Intestinal Hypothesis
Roux-en-Y Gastric Bypass

Duodenal (Jejunal) Bypass

Rubino F, et al
Duodenal (Jejunal) Bypass

• No gastric restriction
• No calorie malabsorption
• No change in food intake
• No change in body weight
Goto-Kakizaki Rat (GK)

Animal Model of Type 2 Diabetes

- Polygenic
- $\beta$-cell defects
- Some insulin resistance
- Non-obese
- Normolipidemic

Most widely used lean model in type 2 diabetes research
42% reduction of AUC (P<0.001)

Rubino F, et al
Ann Surg 239:1

Similar results at 1 week through 9 months after surgery
Duodenal (Jejunal) Bypass

Major, durable ↑ in glucose tolerance with little or no weight loss in several rat DM models (but not in non-DM rats)

F Rubino, D Pacheco, Y Wang, M Speck, Kindel & Tso, others
Does duodenal bypass ameliorate type 2 diabetes in humans?
Resolution of Human Diabetes After Duodenal Bypass


Fasting Glucose

Fasting Insulin
Resolution of Human Diabetes After Duodenal Bypass

Hemoglobin A1c

Body Mass Index

HbA1c (%)

Body Mass Index (kg/m²)

Off all diabetes meds

Months After Surgery

Months After Surgery

Patient 1

Patient 2

Duodenal-Jejunal Bypass in Humans

(“Gastric-Sparing Gastric Bypass”)

Cohen RV, et al.
Prospective Study of DJB for Type 2 DM in Patients With BMI < 35 kg/m$^2$

- 46 patients
- BMI 22–35 kg/m$^2$
- Severe Diabetes
  - Confirmed type 2: negative $\alpha$-GAD, ICA
  - Duration of DM: 2–10 years
  - 70% on insulin; others on oral DM meds
  - Mean HbA1c = 8.9%

Cohen RV, Cummings DE, et al.
Duodenal-Jejunal Bypass in Patients with DM & BMI < 35 kg/m²

Cohen RV, Cummings DE, et al.

HbA1c (%)

Months After Surgery

0 3 6 12

8.9

6.5

100% off insulin Rx

Cohen RV, Cummings DE, et al.
No Relationship Between Change in Body Weight and Improvement in Glycemia

HbA1c

Data at 1 year

Cohen RV, Cummings DE, et al.
Ileal Interposition + Sleeve Gastrectomy

Equal Weight Loss

35% 81%
HbA1c <6%  HbA1c <6%

DePaula et al
SOARD 6:296 (2010)
Can the same thing be accomplished with an endoscopically implantable device?
Duodenal/Jejunal Bypass

- Duodenum + 1/3 Jejunum

Intraluminal Duodenal Sleeve

- Only Duodenum
Duodenal Sleeve

Mucosa isolated from nutrients

Mucosa exposed to nutrients
GK Rats (diabetic)

Complete tube (n=12)
Fenestrated tube (n=12)
No tube (Sham) (n=6)

2 & 3 pair-fed to 1
Complete Duodenal Sleeve
Fenestrated Duodenal Sleeve
Duodenal Sleeve

• No change in D-xylose absorption test
  – Indicates no carbohydrate malabsorption

• No difference from controls in GLP-1 response to oral nutrient load
STOMACH
- Ghrelin
- Leptin
- GRP, NMB

PANCREAS
- Amylin
- Enterostatin
- Glucagon
- Insulin
- PP

What about GIP?

DUODENUM
- CCK, GIP

JEJUNUM
- APOAIV

ILEUM
- GLP1
- Oxyntomodulin
- PYY

COLON
- GLP1
- Oxyntomodulin
- PYY

Cummings DE & Overduin J
J Clin Invest 2007
Abolished Postprandial GIP Response to Oral Glucose in GK Rats With Duodenal Bypass Sleeve

Minutes After Oral Glucose Load

0 Minutes 30 Minutes

GIP

Complete Fenestrated No Complete Fenestrated No

Sleeve Sleeve Sleeve Sleeve Sleeve Sleeve Sleeve Sleeve
Postoperative Body Weight

![Box plot showing postoperative weight gain for different operations. The plot compares Complete, Incomplete, and Non Op Controls operations. The y-axis represents postoperative weight gain, and the x-axis represents the operation type. The box plot indicates the distribution of weight gain with quartiles and outliers.](image-url)
Preoperative OGTT

Blood Glucose (mg/dl)

- Complete
- Fenestrated
- No tube

Rubino F
Postoperative OGTT: No Sleeve (Sham Surgery)
Postoperative OGTT: Fenestrated Sleeve

Blood Glucose (mg/dl)
Postoperative OGTT: Complete Sleeve

Blood Glucose (mg/dl)

OGTT COMPLETE TUBE - GK rats

<table>
<thead>
<tr>
<th>Time After Glucose Load (min)</th>
<th>Pre-op</th>
<th>Post-op</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>90</td>
<td></td>
<td></td>
</tr>
<tr>
<td>120</td>
<td></td>
<td></td>
</tr>
<tr>
<td>180</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P < 0.001
A Very Instructive Rat

Before Surgery

Rubino F
A Less Successful Rat:
Has a Duodenal Sleeve Leak
Diabetes Resolved 9 Days After the Repair

Rubino F
Duodenal-Jejunal Bypass Sleeve

Substantially improves glucose homeostasis in several rat models of type 2 DM

Food bypasses the duodenum & proximal jejunum, as it does in RYGB

L Kaplan, F Rubino, others
Can an upper intestinal sleeve ameliorate type 2 diabetes in humans?
Duodenal-Jejunal Bypass Sleeve

• **Anchor**
  - Nitinol
  - Large proximal opening
  - Barbs in each direction
  - Retrieval drawstrings

• **Liner**
  - Impermeable fluoropolymer
  - 2 feet long
  - Bypasses duodenum & small amt proximal jejunum
  - Radiopaque (RO) markers

**Humans tested to date:**
~220 implanted, ~160 controls
Duodenal-Jejunal Bypass Sleeve Lowers HbA1c

Sorli C, et al. & GI Dynamics

Baseline HbA1c: 8.9%

Baseline HbA1c: 9.0%

HbA1c (change from baseline)

3 months

7 months

DJBS
Sham

* $P=0.004$ vs. Sham

-0.5%
-1.5%
-2.5%
-3.5%

-0.8%
-1.3%
-2.9%
-0.8%
Body Weight Curves After DJB Sleeve or Sham Endoscopy

Body Weight Change (kg)

Weeks After Implantation

Sorli C, et al. & GI Dynamics
Improved Glucose Tolerance

One Week After DJB Sleeve

Immediate, Durable Lowering of *Fasting* Blood Glucose After Endoluminal Sleeve

Fasting Plasma Glucose Change from Baseline (mg/dL)

Treatment (Weeks)

Sham

ELS
Duodenal-Jejunal Bypass Sleeve for Humans

Substantial improvements in glucose homeostasis, before and out of proportion to weight loss
Duodenal (Jejunal) Exclusion

Lower Intestinal vs. Upper Intestinal Hypothesis
Duodenal (Jejunal) Exclusion

Gastro-jejunal Anastomosis

Rubino F, Cummings DE, et al
Oral Glucose Tolerance

**OGTT GK rats**

- **GK DJB**
- **GK Sham**
- **GK GJ**

**Figure Caption:**

Oral Glucose Tolerance Test (OGTT) results for GK rats. The graph shows glucose levels (mg/dl) over time (min) for different groups: GK DJB, GK Sham, and GK GJ. The data is presented with error bars indicating variability. The graph is sourced from Rubino F, et al, *Ann Surg* 244:741.
Patients: severely obese type 2 diabetics

Remove DM Meds

Tests: meal tolerance tests
FS-IVGTT
hyperinsulinemic clamps (with tracers)

Human RYGB Mechanisms Study

1. Normal Oral Feeding
2. Gastric Feeding With G-tube
3. Normal Oral Feeding
4. RYGB

Hyperglycemic
Normoglycemic?
Hyperglycemic?
Normoglycemic?

DE Cummings & DR Flum
Novel Roles of the Gut to Regulate Hepatic Insulin Sensitivity
Nutrient sensing in the gut regulates insulin secretion & sensitivity

Relating to:
A Model

LAGB

Δ intestinal nutrient sensing & metab

↑ hepatic insulin sensitivity

↑ GLP-1

↑ insulin secretion

↓ body weight

↑ insulin sensitivity

RYGB

↓ body weight

↑ insulin sensitivity

TIME
Weight-Independent Anti-Diabetes Candidate Mechanisms of RYGB

\[
\begin{align*}
\uparrow & \text{GLP-1 (}& \& \text{PYY \\& OXM)} & \uparrow & \text{Bile acids} \\
\downarrow & \text{Ghrelin} & \downarrow & \text{Ceramides} \\
\uparrow & \text{Amylin} & \Delta & \text{in Gut Microbiome} \\
\text{Duodenal factor?} & & \downarrow & \text{Inflamm \\& oxidative stress} \\
\text{Intestinal LCFACoA \\& CCK} & & \downarrow & \text{Branched Chain AA in blood} \\
\text{Intestinal Gluconeogenesis} & & \downarrow & \text{Intestinal SGLT-1} \\
\end{align*}
\]

Others?
What’s the clinical role for RYGB to treat type 2 DM in less obese patients?

• BMI > 40

• BMI > 35 and life-threatening obesity-associated cardiopulmonary complications or severe diabetes

• Approved: RYGB, VBG, Banding
**ADA/EASD Consensus Algorithm for Type 2 DM**

- **Diagnosis**
- **Lifestyle Intervention and Metformin**
  - If $\text{HbA}_1\text{c} \geq 7\%$:
    - *No*
    - *Yes*
  - **Add Basal Insulin** (~most effective)
  - **Add Glitazone** (~no hypoglycemia)
  - **Add Sulfonylurea**
- **Intensify Insulin**
- **Add Basal or intensify insulin**
  - **Intensive insulin + metformin ± glitazone**

- *Check HbA$_1$c every 3 months and act until HbA$_1$c is <7%*
- *Although 3 oral agents can be used, insulin therapy is preferred based on effectiveness and expense*

**Bariatric surgery not mentioned for anyone!**

Nathan D, et al., 2006
Diabetologia 49:1711–21
• Gastric bypass improves diabetes via mechanisms beyond reduced food intake & body weight

• Gastric banding improves diabetes only via its effects on food intake and body weight

Societies Changing Their Names in ~2007 to Include “Metabolic Surgery”

- American Society for *Metabolic* and Bariatric Surgery
- Brazilian Society for Bariatric and *Metabolic* Surgery
- Italian Society for Surgery of Obesity and *Metabolic* Diseases
- Venezuelan Society of Bariatric & *Metabolic* Surgery
- International Federation for Surgery of Obesity and *Metabolic* Diseases
- Asia-Pacific *Metabolic* & Bariatric Surgery Society
Gastric bypass improves diabetes via mechanisms beyond reduced food intake & body weight

Gastric banding improves diabetes only via its effects on food intake and body weight

Gastric bypass should be considered to treat type 2 diabetes in patients with BMI ≥ 30 kg/m²

Distribution of T2DM According to BMI

>50% of patients with diabetes worldwide have BMI <35 kg/m²
Management Algorithm for Metabolic Control in Type 2 Diabetes

**Lifestyle Modification**
- diet modification
- weight control
- physical activity

**Metformin**

**Sulphonylurea**

**Acarbose**

**DPP-4 inhibitor**

**Glitazone**

**Insulin**
- Basal
- Premixed
- Basal Bolus insulin

**Bariatric Surgery**
- BMI > 30 eligible & BMI > 35 prioritized
  - If HbA1c > 7.5% despite optimized conventional therapy, especially if weight is increasing, or if other weight responsive comorbidities are not reaching target on conventional therapy.
What’s the Proper Role for GI Surgery in the Treatment of Type 2 Diabetes?

- Randomized controlled trials are needed
- Randomizing surgery vs. medical care is very difficult
- Nevertheless, pivotal RCTs are on
Randomized controlled trials are needed.

And they’re on their way!
CROSSROADS Trial (an RCT)

Calorie Reduction Or Surgery: Seeking
Remission for Obesity And Diabetes
CROSSROADS Trial

- RCT of T2DM Rx in BMI 30–40

- Standard RYGB & Medical Care  OR

- Intensive Medical–Lifestyle Rx
  - Aerobic exercise
  - Diet (low-calorie, low-fat)
  - State-of-the-art DM Rx per ADA/

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