Remission of Diabetes after Bariatric Surgery

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Division of Metabolic and Weight Loss Surgery
Disclosures

- Allergan: grant support
- Covidien: consulting
Evidences that Bariatric Surgery is Metabolic Surgery

The effects are not limited to weight loss or change in adiposity
Liposuction of the subcutaneous abdominal fat doesn't improve metabolic function

Bariatric Surgery is More than Weight Loss

- Appetite Control
- Glucose and Lipid Metabolism
- Insulin Homeostasis
- Regulatory Peptides

Surgical induced changes in the entero–encefalic endocrine axis (Metabolic Surgery) are part of the explanation.
Pathogenesis of Type 2 DM Circa 1988

PATHOGENESIS OF TYPE 2 DIABETES

- Impaired Insulin Secretion
- Hyperglycemia
  - Increased HGP
  - Decreased Glucose Uptake

DeFronzo RA. Med Clin NA 88:787-835, 2004
The Miracle of Insulin

Patient J.L., December 15, 1922

February 15, 1923
Traditional Mechanisms of Resolution of Diabetes after Bariatric Surgery

1. Decreased Energy Intake
   - Increased Energy Expenditure

2. Weight Loss
   - Decrease in Insulin Resistance

3. Resolution of Diabetes
Metabolic effect of Bariatric Surgery on Type II Diabetes

1. Bariatric Surgery
2. Changes in the entero-encefalic endocrine axis
   - Remission Type II Diabetes
   - Weight Loss
A Modern Understanding of The Pathogenesis of Type 2 DM

- Decreased Insulin Secretion
- Decreased Incretin Effect
- Increased Lipolysis
- Islet—a cell
- Increased Glucagon Secretion
- Increased HGP
- Decreased Glucose Uptake
- Neurotransmitter Dysfunction

HYPERGLYCEMIA

SEPTICIDAL SEPTET
Changes in the Entero-Encefalic-Endocrine Axis after RYGB

Incretin Effect

Caloric Intake

Adipocytes

Entero Encefalic Endocrine Axis

Diabetes Resolutio
Incretins and glycemic control

Ingestion of food

GI tract

Release of incretin gut hormones

Active GLP-1 and GIP

Pancreas

Glucose dependent

⇒ Insulin from beta cells (GLP-1 and GIP)

Insulin increases peripheral glucose uptake

Blood glucose control

↓ Glucagon from alpha cells (GLP-1)
Glucose dependent

Increased insulin and decreased glucagon reduce hepatic glucose output

Glucagon-like peptide -1 (GLP-1)

• Produced by L cells in distal small bowel and colon
• One of the most potent substances to increase insulin secretion from β-cells of the pancreas (incretin effect)
• Insulin response is greater following oral glucose than i.v glucose, despite similar plasma glucose concentration
The Incretin Effect is Reduced in Patients with Type 2 Diabetes

*P ≤ .05 compared with respective value after oral load.

INCRETIN-EFFECT

- Restoration of the incretin response could improve glycemic control in such patients
- Is bariatric surgery the best way to restore such response?
The Beginning of Metabolic Surgery

THE AMELIORATION OF DIABETES MELLITUS FOLLOWING SUBTOTAL GASTRECTOMY

MURRY N. FRIEDMAN, M.D., F.A.C.S., ANTONIO J. SANCETTA, M.D., and GEORGE J. MAGOVERN, M.D., Brooklyn, New York

In 1923, Murlin noted the presence of a substance in extracts of the pancreas which could raise the blood sugar. Subsequently, this hyperglycemic factor was demonstrated and duodenum. Therefore, when subtotal gastrectomy for duodenal ulcer resulted in marked amelioration of the diabetic state in 3 patients at the Brooklyn Veterans Hospi-

Surgery, Gynecology & Obstetrics; February 1955
The Entero-Insular Axis

The Hindgut Theory

- The more rapid delivery of undigested nutrients to the distal bowel upregulates the production of L-cell derivatives like GLP-1

*Mason E. Obes Surg 2005 15, 459-461*
GLP-1 Levels after Meal Stimulation

Torquati et al, Surgical Endoscopy
2011
GLP-1 Area Under the Curve (AUC)

Torquati et al, Surgical Endoscopy 2011
Importance of Body Weight in the Pathogenesis of Type II Diabetes
Hormones that Control Eating
Peptide YY (PYY)

- Is a member of neuropeptide Y (NPY) family
- Secreted by gut mucosal endocrine cells postprandially in proportion to calorie intake
- Powerful appetite suppressant
PYY Levels after Meal Stimulation

Torquati et al, Surgical Endoscopy
2011
PYY Area Under the Curve (AUC)

Torquati et al, Surgical Endoscopy 2011
Ghrelin

- Endogenous growth hormone secretagogue
- Produce primarily by stomach
- An appetite stimulant
Changes in Ghrelin after RYGB

RYGB suppressed serum ghrelin concentration

Cummings et al., NEJM
Leptin

- 16 kD protein encoded by the LEP gene in humans (ob in mice)
- Secreted by adipose tissue in pulsatile fashion and greatest concentrations are measured overnight.
- Plays a key role in regulating energy intake and energy expenditure, including appetite and metabolism
Serum Leptin Levels

- **Obese pre-GBS (n=40):** 59±5 (ng/ml)  
  - **P-value:** 0.001

- **Non-Obese (n=16):** 18±4
  - **P-value:** 0.001

- **Post-GBS (n=12):** 19±6
  - **P-value:** NS

Torquati et al, Surgical Endoscopy 2012
The Adipo-insular Axis

• Epidemiologic/scientific evidence supports the association of visceral adiposity and insulin resistance/diabetes and mortality

Gabriely I. Diabetes 2002
Nielsen S. J Clin Invest, 2004
Relationship Between Visceral Adipose Tissue and Insulin Action

Visceral adipose tissue volume per unit surface area (mL/m²)

Glucose disposal (mg/kg LBM/min)

Women
Men

The Adipo-Insular Axis

Fat-derived peptides – “Adipokines”
Adipokines

- Vascular Disease Related
  - Angiotensinogen
  - PAI-1
- Insulin Resistance Related
  - TNFα
  - IL-6
  - Resistin
  - Visfatin
  - Leptin
  - Adiponectin
  - RBP-4
Adiponectin

- Adiponectin is a 30 kDa protein consisting of four domains.
- Adiponectin is believed to have insulin-sensitizing, anti-atherogenic, and anti-inflammatory actions.
- Circulating adiponectin is decreased in subjects with obesity, type 2 diabetes, hypertension, dyslipidemia, and cardiovascular disease as compared with healthy individuals.
Differential Adiponectin Gene Expression

- **Subcutaneous Fat**
- **Omental Fat**

Obese before GB (n=30)

Post-GB (n=10)

P < 0.01

Torquati, Obesity Surgery 2012
Weight gain induces inflammatory changes in adipose tissue

TNF-α

- Proinflammatory cytokine
- Produced by adipocytes and macrophages in WAT
- Over-expressed in obesity
- Link between TNFα and insulin resistance: alters insulin signaling and MAPK pathways in vitro and in vivo
IL-6

- 10-30% of circulating IL-6 is from WAT
- Highly correlated with body mass and inversely related to insulin sensitivity
- Alters insulin signaling in the liver
- IL-6 KO mice develop mature-onset obesity and glucose intolerance
Adjustable gastric banding

Ghrelin ↑
GLP-1 ↔
PYY ↑
Adiponectin ↓
Leptin ↓
TNF-α ↔
Roux-en-Y gastric bypass

- Ghrelin: Decrease
- Adiponectin: Decrease
- GLP-1: Increase
- Leptin: Decrease
- PYY: Increase
- TNF-α: Decrease
Sleeve gastrectomy

Ghrelin ➔ Adiponectin
GLP-1 ➔ Leptin
PYY ➔ TNF-α
Duodenal Switch

- Ghrelin
- GLP-1
- PYY
- Adiponectin
- Leptin
- TNF-α
Effect of Metabolic Surgery on Glucose Metabolism:
Level 1 Clinical Trials
# Bariatric Surgery Efficacy

<table>
<thead>
<tr>
<th>Author</th>
<th>Procedure</th>
<th>DM Resolution</th>
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<tbody>
<tr>
<td>Pories et al 1995</td>
<td>Gastric Bypass</td>
<td>89%</td>
</tr>
<tr>
<td>Torquati et al 2005</td>
<td>Gastric Bypass</td>
<td>74%</td>
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<tr>
<td>Schauer et al 2003</td>
<td>Gastric Bypass</td>
<td>82%</td>
</tr>
<tr>
<td>Sugerman et al 2003</td>
<td>Gastric Bypass</td>
<td>86%</td>
</tr>
<tr>
<td>Dixon et al 2003</td>
<td>Lap Band</td>
<td>64%</td>
</tr>
<tr>
<td>Rosenthal et al 2008</td>
<td>Sleeve Gastrectomy</td>
<td>63%</td>
</tr>
</tbody>
</table>
Effects of Roux-en-Y Gastric Bypass or Diabetes Support and Education on Insulin Sensitivity and Insulin Secretion in Morbidly Obese Patients With Type 2 Diabetes

Chin Meng Khoo, MD,*† Jiegen Chen, PhD,*† Zehra Pamuklar, MD, PhD,*† and Alfonso Torquati, MD, MSCI*†

### TABLE 1. Baseline Characteristics of Study Participants

<table>
<thead>
<tr>
<th>Variable</th>
<th>DSE</th>
<th>Roux-en-Y Bypass</th>
<th>P</th>
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<tbody>
<tr>
<td>N</td>
<td>31</td>
<td>30</td>
<td></td>
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<tr>
<td>Female, %</td>
<td>67.7</td>
<td>66.7</td>
<td>0.929</td>
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<tr>
<td>Age, yr</td>
<td>47.4 ± 1.5</td>
<td>49.6 ± 1.4</td>
<td>0.292</td>
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<tr>
<td>Weight, kg</td>
<td>114.3 ± 3.1</td>
<td>120.1 ± 3.1</td>
<td>0.186</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>40.1 ± 0.9</td>
<td>43.4 ± 0.8</td>
<td>0.006</td>
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<tr>
<td>Waist circumference, cm</td>
<td>122.7 ± 2.3</td>
<td>130.3 ± 2.2</td>
<td>0.018</td>
</tr>
<tr>
<td>Percent body fat, %</td>
<td>42.0 ± 1.1</td>
<td>44.4 ± 1.1</td>
<td>0.159</td>
</tr>
<tr>
<td>Fat free mass, kg</td>
<td>63.6 ± 15.7</td>
<td>63.0 ± 20.5</td>
<td>0.798</td>
</tr>
<tr>
<td>Trunk fat, %</td>
<td>43.7 ± 1.2</td>
<td>47.4 ± 1.1</td>
<td>0.030</td>
</tr>
<tr>
<td>Fat-to-FFM ratio</td>
<td>0.73 ± 0.03</td>
<td>1.07 ± 0.25</td>
<td>0.159</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>7.51 ± 0.23</td>
<td>7.53 ± 0.23</td>
<td>0.943</td>
</tr>
<tr>
<td>Fasting glucose, mg/dL</td>
<td>149.1 ± 9.2</td>
<td>155.6 ± 8.6</td>
<td>0.607</td>
</tr>
<tr>
<td>Fasting insulin, μU/mL</td>
<td>16.9 ± 2.6</td>
<td>21.9 ± 5.4</td>
<td>0.401</td>
</tr>
<tr>
<td>Insulin sensitivity, mU/L⁻¹·min⁻¹</td>
<td>1.39 ± 0.21</td>
<td>1.48 ± 0.22</td>
<td>0.753</td>
</tr>
<tr>
<td>Acute insulin response, mU⁻¹·min</td>
<td>93.3 ± 28.6</td>
<td>71.7 ± 26.8</td>
<td>0.684</td>
</tr>
<tr>
<td>Disposition index</td>
<td>95.2 ± 27.7</td>
<td>77.6 ± 61.0</td>
<td>0.796</td>
</tr>
<tr>
<td>Glucose effectiveness</td>
<td>11.6 ± 1.0</td>
<td>12.3 ± 1.0</td>
<td>0.626</td>
</tr>
<tr>
<td>Free fatty acid, μmol/L</td>
<td>700.4 ± 31.4</td>
<td>757.6 ± 48.4</td>
<td>0.486</td>
</tr>
<tr>
<td>hsCRP, mg/dL</td>
<td>1.20 ± 0.40</td>
<td>0.86 ± 0.19</td>
<td>0.448</td>
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<tr>
<td>Antidiabetes medication, %</td>
<td></td>
<td></td>
<td>0.875</td>
</tr>
<tr>
<td>Oral agents</td>
<td>71</td>
<td>73</td>
<td></td>
</tr>
<tr>
<td>Insulin therapy</td>
<td>29</td>
<td>27</td>
<td></td>
</tr>
</tbody>
</table>

Values are shown as mean ± SE. P values shown in the right column refer to differences between the Diabetes Support and Education and RYGB groups at baseline. Bold values are statistically significant.

Torquati, Ann Surg. 2013
### Changes Body Composition at 6- and 12-Month: DSE vs. RYGB

<table>
<thead>
<tr>
<th></th>
<th>DSE</th>
<th>RYGB Surgery</th>
<th>P Trend From Baseline to 12 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline to 6 mo</td>
<td>Baseline to 12 mo</td>
<td>Baseline to 6 mo</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>2.1 ± 2.6</td>
<td>0.6 ± 1.0</td>
<td>−29.5 ± 1.3</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>0.1 ± 0.3</td>
<td>0.3 ± 0.4</td>
<td>−10.5 ± 0.6</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>−2.0 ± 1.2</td>
<td>−1.0 ± 1.3</td>
<td>−23.3 ± 1.5</td>
</tr>
<tr>
<td>Percent body fat, %</td>
<td>0.1 ± 0.3</td>
<td>−0.1 ± 0.3</td>
<td>−8.7 ± 0.7</td>
</tr>
<tr>
<td>Fat free mass, kg</td>
<td>0.4 ± 0.5</td>
<td>0.6 ± 0.4</td>
<td>−7.8 ± 0.6</td>
</tr>
<tr>
<td>Trunk fat, %</td>
<td>1.0 ± 0.7</td>
<td>0.0 ± 0.6</td>
<td>−10.7 ± 1.0</td>
</tr>
<tr>
<td>Total fat-to-FFM ratio</td>
<td>0.00 ± 0.05</td>
<td>−0.01 ± 0.01</td>
<td>−0.51 ± 0.26</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>−0.1 ± 0.2</td>
<td>0.4 ± 0.3</td>
<td>−1.2 ± 0.2</td>
</tr>
</tbody>
</table>

Torquati, Ann Surg. 2013
Changes in Glucose Metabolism at 6- and 12-Month: DSE vs. RYGB

Torquati, Ann Surg. 2013
Changes in Glucose Metabolism at 6- and 12-Month: DSE vs. RYGB

- Acute insulin response, μU/mL·min⁻¹
- Insulin sensitivity index, mU/L·min⁻¹
- Disposition index
- Glucose effectiveness, x10⁻³·min⁻¹

Follow-up period: Baseline, 6 mo, 12 mo

- □: RYGB surgery
- ●: Diabetes Support and Education (DSE)
Bariatric Surgery versus Intensive Medical Therapy in Obese Patients with Diabetes

Philip R. Schauer, M.D., Sangeeta R. Kashyap, M.D., Kathy Wolski, M.P.H., Stacy A. Brethauer, M.D., John P. Kirwan, Ph.D., Claire E. Pothier, M.P.H., Susan Thomas, R.N., Beth Abood, R.N., Steven E. Nissen, M.D., and Deepak L. Bhatt, M.D., M.P.H.
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Medical Therapy (N=50)</th>
<th>Gastric Bypass (N=50)</th>
<th>Sleeve Gastrectomy (N=50)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of diabetes — yr</td>
<td>8.9±5.8</td>
<td>8.2±5.5</td>
<td>8.5±4.8</td>
<td>0.72</td>
</tr>
<tr>
<td>Use of insulin — no. (%)</td>
<td>22 (44)</td>
<td>22 (44)</td>
<td>22 (44)</td>
<td>1.00</td>
</tr>
<tr>
<td>Age — yr</td>
<td>49.7±7.4</td>
<td>48.3±8.4</td>
<td>47.9±8.0</td>
<td>0.46</td>
</tr>
<tr>
<td>Female sex — no. (%)</td>
<td>31 (62)</td>
<td>29 (58)</td>
<td>39 (78)</td>
<td>0.08</td>
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<tr>
<td>Body-mass index†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Value</td>
<td>36.8±3.0</td>
<td>37.0±3.3</td>
<td>36.2±3.9</td>
<td>0.42</td>
</tr>
<tr>
<td>&lt;35 — no. (%)</td>
<td>19 (38)</td>
<td>14 (28)</td>
<td>18 (36)</td>
<td>0.54</td>
</tr>
<tr>
<td>Body weight — kg</td>
<td>106.5±14.7</td>
<td>106.7±14.8</td>
<td>100.8±16.4</td>
<td>0.10</td>
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<tr>
<td>Waist circumference — cm</td>
<td>114.5±9.4</td>
<td>116.4±9.2</td>
<td>114.0±10.4</td>
<td>0.43</td>
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<tr>
<td>Waist-to-hip ratio</td>
<td>0.95±0.09</td>
<td>0.96±0.07</td>
<td>0.96±0.09</td>
<td>0.88</td>
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<tr>
<td>White race — no. (%)</td>
<td>37 (74)</td>
<td>37 (74)</td>
<td>36 (72)</td>
<td>0.97</td>
</tr>
<tr>
<td>Smoker — no./total no. (%)</td>
<td>15/42 (36)</td>
<td>20/50 (40)</td>
<td>11/50 (22)</td>
<td>0.14</td>
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<tr>
<td>Metabolic syndrome — no. (%)</td>
<td>46 (92)</td>
<td>45 (90)</td>
<td>47 (94)</td>
<td>1.00</td>
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<tr>
<td>History of dyslipidemia — no./total no. (%)</td>
<td>36/43 (84)</td>
<td>44/50 (88)</td>
<td>40/50 (80)</td>
<td>0.55</td>
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<tr>
<td>History of hypertension — no./total no. (%)</td>
<td>26/43 (60)</td>
<td>35/50 (70)</td>
<td>30/50 (60)</td>
<td>0.51</td>
</tr>
</tbody>
</table>
**Effect on Glucose Metabolism**

<table>
<thead>
<tr>
<th>Value at Visit</th>
<th>Intensive medical therapy</th>
<th>Roux-en-Y gastric bypass</th>
<th>Sleeve gastrectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>8.9</td>
<td>9.3</td>
<td>9.5</td>
</tr>
<tr>
<td>3 months</td>
<td>7.7</td>
<td>6.8</td>
<td>7.1</td>
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<tr>
<td>6 months</td>
<td>7.1</td>
<td>6.3</td>
<td>6.7</td>
</tr>
<tr>
<td>9 months</td>
<td>7.4</td>
<td>6.4</td>
<td>6.7</td>
</tr>
<tr>
<td>12 months</td>
<td>7.5</td>
<td>6.4</td>
<td>6.6</td>
</tr>
</tbody>
</table>

**Change in Glycated Hemoglobin**

- **P<0.001**

**Change in Fasting Plasma Glucose**

- **P=0.02**
- **P=0.001**

<table>
<thead>
<tr>
<th>Value at Visit</th>
<th>Baseline</th>
<th>3 months</th>
<th>6 months</th>
<th>9 months</th>
<th>12 months</th>
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<tr>
<td>Intensive medical therapy</td>
<td>155</td>
<td>122</td>
<td>113</td>
<td>120</td>
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<tr>
<td>Roux-en-Y gastric bypass</td>
<td>193</td>
<td>109</td>
<td>96</td>
<td>96</td>
<td>99</td>
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<tr>
<td>Sleeve gastrectomy</td>
<td>164</td>
<td>118</td>
<td>104</td>
<td>102</td>
<td>97</td>
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</tbody>
</table>
Effect on Meds usage and BMI

C Average No. of Diabetes Medications

D Change in BMI

<table>
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<tr>
<th>Value at Visit</th>
<th>2.8</th>
<th>3.1</th>
<th>3.1</th>
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<td>Value at Visit</td>
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<td>Intensive medical therapy</td>
<td>2.6</td>
<td>1.1</td>
<td>0.6</td>
<td>0.4</td>
<td>0.3</td>
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<tr>
<td>Roux-en-Y gastric bypass</td>
<td>2.4</td>
<td>1.1</td>
<td>0.9</td>
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<tr>
<td>Sleeve gastrectomy</td>
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<table>
<thead>
<tr>
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<td>Intensive medical therapy</td>
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<td>31.8</td>
<td>28.2</td>
<td>26.9</td>
<td>26.8</td>
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<td>31.3</td>
<td>28.3</td>
<td>27.3</td>
<td>27.2</td>
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<tr>
<td>Sleeve gastrectomy</td>
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</table>
Prevention is indeed better than cure when it comes to obesity.