Treating Type 2 Diabetes with Bariatric Surgery

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Number (in Millions) of Persons with Diagnosed Diabetes, United States, 1980–2005

The number of Americans with diabetes increased from 5.6 to 15.8 million.

Press Release
For Immediate Release
June 24, 2008
Contact: CDC Division of Media Relations
(404) 639-3286

Number of People with Diabetes Increases to 24 Million

Diabetes now affects nearly 24 million people in the United States, an increase of more than 3 million in approximately two years, according to new 2007 prevalence data estimates released today by the Centers for Disease Control and Prevention (CDC). This means that nearly 8 percent of the U.S. population has diabetes.


Goal of Treating T2DM

Remission of T2DM with Bariatric

1. Normoglycemia
2. Medication Discontinuation
3. Prevent End-organ Damage
4. Decrease Diabetes Related Death
Medical Therapy for Type 2 Diabetes Mellitus (T2DM)

- Most address a single aspect of the pathophysiologic defect – glycemic control
- Goal is reduce HbA1c to < 6 to 7% (achieved with Medical therapy in 37%)

• **Oral Agents:**
  - α-glucosidase inhibitors
  - biguanides (metformin)
  - meglitinides
  - thiazolidinediones
  - sulfonylureas
  - Dipeptidyl peptidase-IV (DPP-IV) inhibitors
  - Prevent breakdown of endogenous GLP-1
  - Sitagliptin (Januvia™) (100 or 200 mg/d PO)
  - Vildagliptin (Galvus®)

• **Injectable Agents:**
  - Insulin
  - Glucagon-like peptide-1 (GLP-1) analogues
    - Exenatide (Byetta™)
  - Liraglutide
  - 0.65–1.90 mg/d SQ
  - Dipeptidyl peptidase-IV (DPP-IV) inhibitors
  - Sitagliptin (Januvia™) (100 or 200 mg/d PO)
  - Vildagliptin (Galvus®)

Bariatric Surgery, Weight Loss and Insulin Resistance

Several bariatric surgical techniques originally designed to promote weight loss offer a variable but impressive rate of cure for T2DM.

Bariatric operations that result in greater weight loss are associated with greater rates of T2DM cure.

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<th>% EWL: Band, RYGB, BPD/DS</th>
<th>Resolution of diabetes: Band, RYGB, BPD/DS</th>
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<td>621 Studies – 135,246 patients</td>
<td>19 Studies – 11,175 patients</td>
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</table>

Distribution of Deaths and Death Rates per 10,000 Person-Years, According to Study Group

Original Article

Long-Term Mortality after Gastric Bypass Surgery
Ted D. Adams, Ph.D., M.P.H., et al
University of Utah School of Medicine
Salt Lake City, UT
N Engl J Med
Volume 357(8):753-761
August 23, 2007

Original Article

Effects of Bariatric Surgery on Mortality in Swedish Obese Subjects
Lars Sjöström, M.D., Ph.D., et al.
Swedish Obese Subjects (SOS) Study
Sahlgrenska University Hospital, Gothenburg, Sweden,
N Engl J Med
Volume 357(8):741-752
August 23, 2007
Mechanisms Resolution Diabetes RYGB

- Decrease in fat mass (liver, abdomen, periphery)
- Calorie restriction, negative energy balance
- Decrease in adipocytokines and other cytokines
- Altered gut hormone secretion (GLP-1, GIP, CCK, Ghrelin, PYY, Somatostatin, etc)
- Altered pancreatic hormone secretion (Insulin, Glucagon, PPP)
- Altered glucose kinetics
- Improvement in pancreatic beta cell function, slow apoptosis
- Improvement of associated diseases and stressors
- Hepatic glucose production
- Altered gastric emptying, nutrient intake, particles size and absorption
- Others

GLucose Metabolism - Incretins

GLP-1 (glucagon-like peptide-1)
- L cells in the distal portion of small bowel
  - Promotes insulin secretion stimulated by oral glucose
  - Reduces hepatic glucose production
  - Decelerates gastric emptying
  - Stimulates β-cell neogenesis, regeneration, replication and slows apoptosis
  - Promotes strong suppression of glucagon secretion

GIP (Glucose-dependent insulinoitropic polypeptide/gastric inhibitory polypeptide)
- Released duodenum and proximal small bowel – K cells in response to glucose and fat
  - Promotes insulin secretion stimulated by oral glucose.
  - In Type 2 DM - reduction in the insulin secretory response to hyperglycemia
  - In Euglycemia stimulates Glucagon and does not affect gastric emptying
Whether or to what degree the altered patterns of gut and pancreatic hormone secretion bolster beta cell function and improve peripheral glucose disposal, insulin resistance and T2DM independent of weight loss.
PATIENTS AND METHODS

• 22 morbidly obese subjects with insulin resistance
• RYGB (n=12) with caloric restriction vs. and calorie restriction (DIET) alone (n=10)
• Subjects studied before and after 15 days while on identical 800 kcal diet (Optifast)
• 6 months after Gastric Bypass – RYGB group only

• Fasting measurements: glucose, insulin, HOMA-IR
• Euglycemic hyperinsulinemic clamp (insulin infusion rate 40 mU/m²):
  M-Value - peripheral glucose uptake/disposal
  Serum insulin levels during the clamp
• 3-hour meal test (300 kcal; 50% CHO, 30% protein, 20% fat):
  Insulin, GLP-1, and GIP levels

CHARACTERISTICS OF THE GROUPS AT BASELINE

<table>
<thead>
<tr>
<th></th>
<th>RYGB (n=12)</th>
<th>Diet Only (n=10)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female/Male</td>
<td>9 F; 3 M</td>
<td>6 F; 4 M</td>
<td>0.65</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>47.4 ± 8.7</td>
<td>40.2 ± 13.4</td>
<td>0.16</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>48.4 ± 6.8</td>
<td>48.3 ± 6.6</td>
<td>0.99</td>
</tr>
<tr>
<td>% Excess body weight</td>
<td>55.4 ± 6.4</td>
<td>55.3 ± 6.8</td>
<td>0.96</td>
</tr>
<tr>
<td>% Fat (by DEXA)</td>
<td>48.6 ± 6.8</td>
<td>46.8 ± 4.7</td>
<td>0.53</td>
</tr>
</tbody>
</table>
**PERIPHERAL GLUCOSE UPTAKE (M-VALUE)**

AT BASELINE

- In contrast to the decreases seen in fasting glucose and insulin levels, there was virtually no change in the amount of glucose taken up in the periphery during the euglycemic hyperinsulinemic clamp (M-value).
- M-values remained below the boundary for the lowermost quartile of values in healthy control subjects (green line).

**CHANGES IN WEIGHT AND BODY COMPOSITION**

**FASTING GLUCOSE, INSULIN, HOMA-IR**

<table>
<thead>
<tr>
<th></th>
<th>RYGB</th>
<th>DIET</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight loss (kg)</td>
<td>9.9 ± 2.4</td>
<td>8.2 ± 2.3</td>
<td>0.11</td>
</tr>
<tr>
<td>% excess weight loss</td>
<td>12.7 ± 2.4</td>
<td>10.9 ± 2.8</td>
<td>0.12</td>
</tr>
<tr>
<td>% of weight lost as fat</td>
<td>40 ± 6</td>
<td>30 ± 17</td>
<td>0.22</td>
</tr>
<tr>
<td>Fasting glucose (mg/dL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>baseline</td>
<td>89 ± 8</td>
<td>96 ± 12</td>
<td>0.18</td>
</tr>
<tr>
<td>Δ fasting glucose after 15 days</td>
<td>-10 ± 10*</td>
<td>-14 ± 11*</td>
<td>0.47</td>
</tr>
<tr>
<td>Fasting insulin (µU/mL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>baseline</td>
<td>21.1 ± 15.0</td>
<td>30.7 ± 14.6</td>
<td>0.25</td>
</tr>
<tr>
<td>Δ fasting insulin after 15 days</td>
<td>-7.5 ± 8.3*</td>
<td>-10.3 ± 7.7*</td>
<td>0.50</td>
</tr>
<tr>
<td>HOMA-IR at baseline</td>
<td>4.3 ± 2.0</td>
<td>6.5 ± 2.6</td>
<td>0.09</td>
</tr>
<tr>
<td>Δ fasting insulin after 15 days</td>
<td>-1.2 ± 1.6*</td>
<td>-1.9 ± 1.0*</td>
<td>0.30</td>
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Data are mean ± SD; *P ≤ 0.02 vs baseline by paired t-test

**MEAN INSULIN LEVELS DURING EUGLYCEMIC HYPERINSULINEMIC CLAMP BEFORE AND 15 DAYS AFTER BYPASS OR CALORIC RESTRICTION**

Steady-state insulin levels, measured during the clamp, decreased in the RYGB group to a greater extent than with caloric restriction.

Campos GM et al. ADA June 27, 2009
SERUM INSULIN DURING MEAL TEST (BASELINE VS. 15 DAYS)

Insulin levels at 15 days after RYGB increased at 30 min post-meal (P=0.01 vs. baseline and vs. Diet group)

GLP-1 DURING MEAL TEST (BASELINE VS. 15 DAYS)
Change in AUC GLP-1 15 days after RYGB was highly significant (P<0.01 vs. baseline and vs. change in Diet Group)

CHANGES IN PERIPHERAL GLUCOSE UPTAKE (M-VALUE) WERE OBSERVED 6 MONTHS AFTER RYGB AND CORRELATED WITH THE MAGNITUDE OF WEIGHT LOSS

SUMMARY OF RESULTS
15 days after either RYGP vs. DIET alone:
- Modest and similar changes in weight and body composition
- Similar decreases fasting glucose, insulin levels and HOMA-IR
- Virtually no change in peripheral glucose uptake
- Serum insulin levels during clamp decreased in RYGB group, suggesting increased insulin clearance
- Altered pattern of GLP-1, GIP and insulin secretion meal test in RYGB

6 months after RYGB:
- Significant improvement in peripheral glucose uptake
- Changes in peripheral glucose uptake correlated significantly with magnitude of weight lost
CONCLUSIONS

a) Short-term metabolic changes after RYGB cannot be explained by caloric restriction alone.

b) Improvement in peripheral glucose uptake after RYGB is observed only after substantial weight loss and correlates with the magnitude of weight loss.

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Executive Summary: Standards of Medical Care in Diabetes—2009

Bariatric Surgery

- Bariatric surgery should be considered for adults with BMI ≥35 kg/m² and type 2 diabetes, especially if the diabetes is difficult to control with lifestyle and pharmacologic therapy. (B)
- Patients with type 2 diabetes who have undergone bariatric surgery need lifelong lifestyle support and medical monitoring. (E)
- Although small trials have shown glycemic benefit of bariatric surgery in patients with type 2 diabetes and BMI of 30–35 kg/m², there is currently insufficient evidence to generally recommend surgery in patients with BMI <35 kg/m² outside of a research protocol. (E)

The Diabetes Surgery Summit Consensus Conference

Recommendations for the Evaluation and Use of Gastrointestinal Surgery to Treat Type 2 Diabetes Mellitus

Francesco Rubino, MD,⁎ Lee M. Kaplan, MD, PhD,† Philip R. Schauer, MD,‡ and David E. Cummings, MD,‖ On Behalf of the Diabetes Surgery Summit Delegates
Whereas diabetes is traditionally viewed as a chronic, relentless disease in which delay of end-organ complications is the major treatment goal, GI surgery offers a novel end point: the concept of complete disease remission.

The role for GI surgery in diabetes treatment, however, is not clearly defined.

Growing evidence suggests that the antidiabetic impact of these operations cannot be explained by their effects on food intake and body weight alone.

Clinicians are performing GI operations to treat diabetes without clear parameters or indications sufficiently supported by scientific evidence. This emerging practice includes not only the use of conventional bariatric procedures but also experimental new GI operations that have often not been adequately tested in animals before being applied to humans.

Conversely, given that certain operations cause complete remission of T2DM in a substantial number of cases and can reduce mortality attributed to diabetes, it may be clinically appropriate to expand the indications for these procedures to patients with diabetes who do not meet existing obesity-based criteria for bariatric surgery.

**GOALS OF THE DIABETES SURGERY SUMMIT**

- Review impact on T2DM of established bariatric and experimental GI operations
- Discuss plausible mechanisms GI operations might ameliorate T2DM independent of CR/WL

**Attempt:**
- Identify indications and contraindications for GI surgery to treat T2DM
- Develop Recommendations for Clinical Studies
- Define role of surgery in the broader medical strategy for diabetes care

**Methods**

- Multidisciplinary group of 50 delegates
- Current scientific evidence examined and critiqued
- Consensus statements were formed
- The statements were formally critiqued by representatives of several scientific societies
- A formal position statement was created
Position Statement

• Bariatric surgery should be considered for the treatment of T2DM in acceptable surgical candidates with BMI > 35 (A).
• Surgical approach may also be appropriate as a non-primary alternative to treat inadequately controlled T2DM in BMI 30-35 (B) RYGB may be appropriate (C)
• Novel GI surg techniques should only be used in IRB-approved trials and registered trials (A)

(A)=90-100% agreement  (B)=78-89% agreement  (C)=67-77% agreement.

Position Statement

• Development of standards for measuring clinical and physiological outcomes of surgical treatment for T2DM is a high priority (A)
• Randomized controlled trials to assess utility of surgery for T2DM in BMI <35 (A)
• Development of a standard registry/database is a high priority for research (A)

(A)=90-100% agreement  (B)=78-89% agreement  (C)=67-77% agreement.

Position Statement

• Collaboration among endocrinologists, surgeons, and basic scientists encouraged to facilitate understanding of GI mechanisms of metabolic regulation (A)
• Establishment of a multidisciplinary taskforce to guide the study and development of diabetes surgery is a high priority (A)

(A)=90-100% agreement  (B)=78-89% agreement  (C)=67-77% agreement.