Learning Objectives

1. Summarize the epidemiology, impact, and pathophysiology of obesity and type 2 diabetes mellitus
2. Explain the mechanisms of weight loss associated with the different forms of bariatric surgery
3. Identify possible limitations for the use of bariatric surgery in type 2 diabetes mellitus
4. Propose evidence-based indications for the use of bariatric surgery for the remission of type 2 diabetes mellitus
I. Obesity
   a. Epidemiology
      i. 1.1 billion overweight adults worldwide, including 312 million who are obese
      ii. More than one-third (35.7%) of U.S. adults are obese

   
   Table 1: Classification of Obesity
   
<table>
<thead>
<tr>
<th>BMI (kg/m²)</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 18.5</td>
<td>Underweight</td>
</tr>
<tr>
<td>18.5 - 24.9</td>
<td>Normal Weight</td>
</tr>
<tr>
<td>25.0 - 29.9</td>
<td>Overweight</td>
</tr>
<tr>
<td>30 - 34.9</td>
<td>Class I Obesity</td>
</tr>
<tr>
<td>35.0 - 39.9</td>
<td>Class II Obesity (Severe Obesity)</td>
</tr>
<tr>
<td>&gt; 40.0</td>
<td>Class III Obesity (Morbid Obesity)</td>
</tr>
</tbody>
</table>

   * Body Mass Index (BMI) = kilograms / meters²

   b. Impact
      i. Direct medical costs of $147 billion per year in the US
      ii. Direct medical costs $1,429 higher per year in obese patients compared to normal weight individuals

   c. Complications
      i. 5x higher risk of hypertension
      ii. 3.6x higher risk of coronary artery disease
      iii. 10% of cancer related deaths among non-smokers

II. Type 2 Diabetes Mellitus
   a. Epidemiology
      i. 25.8 million Americans with type 2 diabetes mellitus (8.3% of the U.S. population)
      ii. U.S. prevalence doubled in past 25 years, and continues to increase

   b. Impact
      i. Total U.S. health care expenditure of $174 billion in 2010
      ii. Total estimated annual cost of $12 billion in Texas
      iii. Estimated total lifetime US cost of $172,000 in person diagnosed with diabetes at age 50 and $305,000 diagnosed at age 30
      iv. Over 60% of total medical costs incurred within 10 years of diabetes diagnosis

   c. Complications
      i. Leading cause of end-stage renal disease (44%)
      ii. Leading cause of blindness (28.5%) in adults age 20-74
      iii. Leading cause of nontraumatic lower-limb amputations (60%)

   d. Treatment Goals
      i. Current ADA/AACE recommendations are to reduce A1c to <6.5% to <8% utilizing medications and lifestyle changes to reduce/prevent complications of diabetes
      ii. Remission
         1. Partial: A1c < 6.5% and fasting blood glucose (FBG) 100 – 125 mg/dL for one year without pharmacological therapy
2. Complete: A1c < 6.5% and FBG < 100 mg/dL for one year without pharmacological therapy
3. Prolonged: Complete remission for five years without pharmacological therapy

III. Diabesity
   a. Risk of developing type 2 diabetes increased 93-fold in women and 42-fold in men who are severely obese compared to healthy weight individuals\(^8,9\)
   b. Obesity represents a state of insulin resistance\(^10\)
      i. Obesity in non-diabetics associated with 29% decline in insulin sensitivity
      ii. Further 28% decline in insulin sensitivity with progression to impaired fasting glucose
      iii. Central obesity associated with more insulin resistance than lower body obesity\(^11\)
   c. Pathophysiology of lipotoxicity\(^12,13\)
      i. Randle Cycle
         1. Glucose and Free Fatty Acid (FFA) compete for oxidative substrate in muscle
         2. ↑FFA = ↓glucose utilization
      ii. Elevated FFA levels impair insulin secretion, increase gluconeogenesis, and induce hepatic and muscle cell insulin resistance

IV. Glucagon-Like Peptide-1 in Type 2 Diabetes\(^14,15\)
   a. Released from neuroendocrine L cells of distal ileum in response to carbohydrate/fat ingestion
   b. Pharmacological properties
      i. Potentiates insulin secretion from β cells of pancreas
      ii. Decreases glucagon secretion
      iii. Delays gastric emptying and increases satiety
   c. Rapidly degraded by dipeptidyl peptidase IV (DPP-IV) with elimination \(t_{1/2}\) of 2 minutes
   d. Endogenous GLP-1 reduced in patients with type 2 diabetes as well as obese non-diabetics\(^16,17\)
   e. GLP-1 receptor agonists\(^18\)
      i. Provide supratherapeutic levels of GLP-1
      ii. Provide A1c reduction of 1-1.5%
      iii. Weight loss of 2-3 kg
      iv. Exenatide
         1. Shares 50% homology to endogenous GLP-1
         2. Resistant to breakdown of DPP-IV through added glycine and NH\(_2\) group
         3. Increase elimination \(t_{1/2}\) of 3-4 hours
      v. Liraglutide
         1. Shares 97% homology to endogenous GLP-1
         2. Resistant to breakdown of DPP-IV through fatty acid side chain enabling albumin binding
         3. Increased elimination \(t_{1/2}\) of 11-15 hours
Table 2: Appetite Regulation Hormones

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Effect</th>
<th>Produced By</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucagon Like Peptide-1 (GLP-1)</td>
<td>Increased satiety, insulin secretion, glucagon suppression, slows gastric emptying</td>
<td>L-cells of ileum in response to feeding</td>
</tr>
<tr>
<td>Peptide YY (PYY)</td>
<td>Increased satiety, slows gastric emptying</td>
<td>Neuroendocrine cells of the ileum and colon in response to feeding</td>
</tr>
<tr>
<td>Cholecystokinin (CCK)</td>
<td>Increased satiety, slows gastric emptying, stimulates digestion of fat/protein</td>
<td>L-cells of small intestine</td>
</tr>
<tr>
<td>Leptin</td>
<td>Increased satiety</td>
<td>White adipose tissue in proportion to total amount of body fat</td>
</tr>
<tr>
<td>Ghrelin</td>
<td>Increased hunger</td>
<td>Fundus of stomach and epsilon cells of pancreas</td>
</tr>
</tbody>
</table>

V. Appetite-Regulating Hormone Homeostasis

a. Feeding state
   i. Release of PYY, GLP-1, CCK, leptin from gut mucosa to increase satiety and utilize glucose/fat
   ii. Inhibition of ghrelin release

b. Fasting state
   i. Release of ghrelin from stomach to stimulate hunger
   ii. Inhibition of PYY, GLP-1, CCK, and leptin

Diagram 1: Appetite Regulation Hormone Diagram

**Agp (Agouti-related protein), NYP(Neuropeptide-Y): Hunger inducing proteins
***POMC (Pro-opiomelanocortin): Appetite suppressing protein
VI. Hormonal Adaptations to Weight Loss
   a. Short term disturbances in appetite hormones following weight loss
      i. Reduction in leptin at 3, 6, and 12 weeks during weight loss 20
      ii. 25% increase in 24 hour ghrelin levels following 17% weight loss at six months 21
      iii. Reduction in CCK 10 weeks after 10% weight loss 22
      iv. Increased hunger shown with increased ghrelin, and decreased leptin, respectively 20, 21
   b. Disturbances in appetite hormones persist for at least one year after weight loss 23
      i. Obese non diabetics receiving 8 weeks of meal replacement and exercise counseling
         1. Weight loss of 13.5 kg at 10 weeks, 8 kg weight loss maintained at one year
         2. Reduction of leptin, PYY, GLP-1 and increase of ghrelin from baseline at one year
      ii. Increase in hunger and desire to eat food from baseline at one year

VII. Pharmacologically Induced Weight Loss
   a. Weight loss with pharmacological products minimal at one year
      i. Lorcaserin: 5 – 6 kg weight loss 24
      ii. Orlistat: 2 – 3 kg weight loss 25
      iii. Rimonabant: 4 – 5 kg weight loss 26
      iv. Sibutramine: 5 – 6 kg weight loss 26
      v. Diethylpropion: 3 – 4 kg weight loss 27
      vi. Phentermine: 3 – 4 kg weight loss (at 6 months) 27
      vii. Phentermine/topiramate: 8 – 10 kg weight loss 28
      viii. GLP-1 agonists: 2 – 3 kg weight loss 18
   b. Sibutramine, rimonabant, orlistat show minimal reduction of A1c (-0.25-0.75%) in diabetics 29
VIII. **National Institutes of Health Recommendations for Bariatric Surgery**

a. Recommended in obese patients with a BMI ≥ 40 kg/m²
b. Recommended in obese patients with a BMI ≥ 35 kg/m² and serious coexisting medical conditions

IX. **Types of Bariatric Surgery**

a. Malabsorptive Bariatric Surgery
   i. Bypasses major portions of stomach and proximal intestine, causing malabsorption
   ii. Increased chance of nutritional and metabolic complications
   iii. Examples: biliopancreatic diversion, jejunoileal bypass

b. Restrictive Bariatric Surgery
   i. Reduces amount of oral intake and produces early satiety
   ii. Low risk of metabolic or nutritional complications as alimentary canal is left intact
   iii. Examples: gastric banding, sleeve gastrectomy

c. Mixed Bariatric Surgery
   i. Applies both techniques of restriction and malabsorption
   ii. Examples: roux-en-Y gastric bypass (RYGB), biliopancreatic diversion with duodenal switch

X. **Laparoscopic Gastric Banding**

a. Inflatable silicon band placed in proximal portion of stomach
b. Slows and limits delivery and of food that can be consumed at one time

XI. **Vertical Sleeve Gastrectomy**

a. 75% of stomach removed
b. Open edges attached together with surgical staples
c. Forms stomach in the shape of a “sleeve” or tube with a banana shape
XII. Roux – en-Y Gastric Bypass (RYGB)  
   a. “Gold standard”  
   b. Separation of upper “gastric pouch” from remnant stomach  
   c. Small intestine divided in the middle of jejunum  
   d. Anastomosis of gastric pouch to distal jejunum, bypassing remnant stomach and upper duodenum  
   e. Remnant stomach and proximal jejunum anastomosed further down jejunum  

XIII. Biliopancreatic Diversion/Duodenal Switch  
   a. Sleeve gastrectomy performed in which 75% of stomach removed and open edges stapled together  
   b. Small intestine divided in two places in the proximal small intestine (duodenum) and the distal small intestine (ileum)  
   c. Proximal end of ileum is connected to proximal end of duodenum, effectively bypassing the duodenum and jejunum  
   d. Distal end of duodenum re-connected in the ileum  

IX. Complications of Bariatric Surgery  
   a. Metabolic complications  
      i. “Dumping” syndrome  
         1. Bypass of undigested products causes hyperosmolarity of intestinal components  
         2. Fluid drawn into intestine leads to hypotension, intestinal distension, cramping  
         3. Occurs 30-60 minutes after calorie dense meal (high in sugar content)  
         4. Occurs in 70% of patients, transiently during first year post malabsorptive surgery primarily  
         5. Treatment: small, frequent meals, avoidance of simple sugars, avoidance of liquids 30 minutes before and after solid food  
      ii. Hyperinsulinemic hypoglycemia  
         1. Severe hypoglycemia after mixed meal in patients post malabsorptive procedures primarily  
         2. Exaggerated incretin response causing increased first-phase insulin secretion  
         3. Potential cause of pancreatic cell hyperplasia (nesidioblastosis)  
         4. Occurs 2-4 years post malabsorptive surgery, rare occurrence (<1%)  
         5. Treatment: acarbose to slow breakdown and absorption of complex carbohydrates
b. Nutritional complications
   i. Protein-calorie malnutrition
      1. Intolerability of red meat and other protein products
      2. Reported in 7-12% of all patients post bariatric surgery
      3. Causes hypoalbuminemia in 20% of all patient at 6 months
      4. Treatment: Increased non red meat protein intake (dairy, fish, eggs), oral supplementation, parenteral nutrition
   ii. Fat malabsorption
      1. Decreased absorptive surface in stomach results in diarrhea and steatorrhea
      2. Decrease fat-soluble vitamin (Vitamins A, D, E, K) absorption
         a. Deficiency incidence of 69% (Vit A), 68% (Vit K), 63% (Vit D) at four years post surgery
      b. Treatment: all patients post bariatric surgery require supplementation indefinitely
   iii. Micronutrient deficiencies (up to 70% of patients following malabsorptive procedures primarily)
      1. Vitamin B12 deficiency → bypass of stomach-secreting acid which frees B12 from food
      2. Iron deficiency anemia → bypass of acidic stomach which reduces iron from ferric to ferrous state for absorption in duodenum and jejunum
      3. Folate deficiency → bypass of absorption site (proximal small intestine)
      4. Calcium deficiency → decreased intake of calcium-containing food, bypass of absorption site (duodenum, jejunum), decreased vitamin D mediated absorption
      5. Thiamine deficiency → bypass of absorption site (proximal small intestine)
   c. Cholelithiasis
      i. Rapid weight loss increases sludge and gallstone formation
      ii. Reported in 30% of all patients 6 months after surgery
      iii. Treatment: ursodiol therapy required for 6 months after bariatric surgery
   d. Serious complications
      i. Mortality of 0.35% at two years post surgery (similar to laparoscopic cholecystectomy)
      ii. 21% decline in serious complications from 2002 to 2006 due to safer laparoscopic procedures
      iii. 4.1% incidence of serious complications within 30 days of procedure
   X. Mortality Benefit
      a. All-cause mortality reduction of 21% in severely obese patients 16 years post bariatric surgery compared to those who received usual care (NNT =76)
      b. All-cause mortality reduction of 40% in retrospective cohort of 8000 obese patients who underwent gastric bypass compared to age, sex, and BMI-matched controlled subjects.
      c. Reduced cardiovascular deaths and cardiovascular events 15 years post bariatric surgery compared to matched controls who received usual care
XI. **Hypotheses for Diabetic Control Through Bariatric Surgery**  
   a. Foregut exclusion hypothesis  
      i. Nutrient bypass of proximal gut prevents secretion of GIP which promotes insulin resistance  
      ii. Proven invalid as vertical sleeve gastrectomy does not bypass proximal gut, yet still results in diabetes remission and weight loss similar to RYGB and biliopancreatic diversion  
   b. Hindgut hypothesis  
      i. Increased delivery of nutrients to distal ileum causes exaggerated GLP-1/PYY release through overstimulation of neuroendocrine L cells  
      ii. Normalization of blood glucose within months following duodenal switch procedure without restrictive gastric surgery in moderately obese diabetic patients (mean BMI 33 kg/m²)  

XII. **Bariatric Surgery and Appetite Regulating Hormones**  
   a. PYY levels post bariatric surgery dependent on specific procedure  
      i. Increased fasting and meal-stimulated PYY levels following RYGB and sleeve gastrectomy  
      ii. Increased post-prandial PYY in RYGB but normal in gastric banding  
   b. Mixed results on ghrelin levels post bariatric surgery  
      i. Studies report decreased, similar, and increased 24 hour ghrelin levels post RYGB  
      ii. Increased and unchanged ghrelin levels reported post gastric banding  
      iii. Role of ghrelin undefined at present time  
   c. Leptin levels unchanged post RYGB and sleeve gastrectomy  

XIII. **Bariatric Surgery and Incretin Hormones**  
   a. Increased GLP-1 AUC by factor of 5 one month post RYGB  
   b. Increased GLP-1 peak following meal ingestion by factor of 4 two weeks post RYGB  
   c. GLP-1 AUC tripled one month following biliopancreatic diversion  
   d. Post-prandial GLP-1 increased following RYGB but unchanged following gastric banding  
   e. Persistent post-prandial increases of GLP-1 twenty years after duodenal jejunal bypass  

XIV. **Bariatric Surgery in Type 2 Diabetics**  
   a. Glycemic control achieved within days to months after operation, before major weight loss  
   b. Insulin resistance decreased 67% seven days post RYGB  
   c. Insulin sensitivity fully normalized in morbidly obese diabetic and insulin resistant patients after biliopancreatic diversion  
   d. Insulin secretion decreased to match normalization of insulin sensitivity after biliopancreatic diversion  
   e. Average weight loss of 40 kg  
      i. Biliopancreatic diversion = 44 kg weight loss  
      ii. Roux-en-Y gastric bypass = 45 kg weight loss  
      iii. Gastric banding = 32 kg weight loss  
   f. Average remission of type 2 diabetes = 78%  
      i. Biliopancreatic diversion / duodenal switch = 95%  
      ii. Roux-en-Y gastric bypass = 80%  
      iii. Gastric banding = 57%
<table>
<thead>
<tr>
<th>Society</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>American Diabetes Association</strong> 60</td>
<td>• Bariatric surgery may be considered for adults with BMI &gt; 35 kg/m² and type 2 diabetes, especially if the diabetes or associated comorbidities are difficult to control with lifestyle and pharmacologic therapy (level B)</td>
</tr>
<tr>
<td></td>
<td>• Although small trials have shown glycemic benefit of bariatric surgery in patients with type 2 diabetes and BMI 30-35 kg/m², there is currently insufficient evidence to generally recommend surgery in patients with BMI &lt; 35 kg/m² outside of a research protocol (level E)</td>
</tr>
<tr>
<td><strong>American Association of Clinical Endocrinologists</strong> 61</td>
<td>• Consideration may be given to laparoscopic-assisted gastric banding in patients with T2DM who have a body mass index greater than 30 kg/m² or Roux-en-Y gastric bypass for patients with a body mass index greater than 35 kg/m² to achieve at least short-term weight reduction (Grade A)</td>
</tr>
<tr>
<td></td>
<td>• Patients with T2DM who undergo Roux-en-Y gastric bypass must have meticulous metabolic postoperative follow-up because of a risk of vitamin and mineral deficiencies and hypoglycemia</td>
</tr>
<tr>
<td><strong>International Diabetes Federation</strong> 62</td>
<td>• Bariatric surgery is an appropriate treatment for people with Type 2 diabetes and obesity (BMI = 35 kg/m²) not achieving recommended treatment targets with medical therapies, especially where there are other obesity-related co-morbidities.</td>
</tr>
<tr>
<td></td>
<td>• Under some circumstances people with a BMI 30-35 kg/m² should be eligible for surgery</td>
</tr>
</tbody>
</table>
XV. Dixon et al. 63
   a. Published in Journal of the American Medical Association 2008
   b. Two year single-centered prospective randomized controlled trial
   c. Laparoscopic gastric banding + conventional therapy vs. conventional therapy alone
   d. BMI >30 and <40 kg/m², diabetes duration < 2 years, A1c = 7.7%
   e. Diabetes remission defined as: FBG < 126 mg/dL and A1c < 6.2% at two years post randomization without the use of oral hypoglycemics or insulin

XVI. Mingrone et al. 64
   a. Published in New England Journal of Medicine 2012
   b. Two year single-centered prospective randomized controlled trial
   c. RYBG + conventional therapy vs. biliopancreatic diversion + conventional therapy vs. conventional therapy alone
   d. BMI ≥ 35 kg/m², diabetes duration ≈ 6 years, A1c = 8.6%
   e. Diabetes remission defined as: FBG < 100 mg/dL or A1c < 6.5% for one year without medication

XVII. Schauer et al. 65
   a. Published in New England Journal of Medicine 2012
   b. One year single-centered prospective randomized controlled trial
   c. RYBG + intensive medical therapy vs. sleeve gastrectomy + intensive medical therapy vs. intensive medical therapy alone
   d. BMI 27-35 kg/m², diabetes duration = 8 years, A1c = 9.2%
   e. Diabetes remission defined as: A1c < 6% at one year post randomization with or without medications

**Purpose**
- To compare surgically induced weight loss, using laparoscopic adjustable gastric banding (LAGB), with conventional therapy for the management of recently diagnosed type 2 diabetes

**Design**
- Prospective, single center, nonblinded, randomized controlled trial

**Patient Population**
- Inclusion: age 20-60 y/o, BMI >30 and <40 kg/m², diagnosed type 2 diabetes in previous two years with no signs/symptoms of retinopathy or renal impairment
- Exclusion: type 1 diabetes, diabetes secondary to specific disease state (i.e. pancreatitis), previous bariatric surgery, drug or alcohol addiction, recent vascular event (MI/stroke in previous 6 months), internal malignancy, portal hypertension

**Cohorts**
- Laparoscopic gastric banding (LAGB) plus conventional therapy vs. conventional therapy alone

**Outcomes**
- **Primary outcomes:** remission of diabetes at two years post surgery (defined as FBG < 126 mg/dL and A1c < 6.2% without the use of oral hypoglycemics or insulin)
- **Secondary outcomes:** change in A1c, body weight, blood pressure, fasting lipids, medication use, indirect measures of insulin resistance using the homeostatic model

**Methods**
- Conventional Therapy
  - Visit every 6 weeks throughout two year study with either: general physician, nurse, dietitian, and diabetes educator
  - Pharmaceutical agents determined by experienced diabetologist
  - Individually constructed lifestyle programs for dietary counseling
  - Physical activity encouraged
  - No use of TZD’s or exenatide as not available at the time
- Bariatric Surgery
  - LAGB performed by one of two surgeons within one month of randomization
  - Progress reviewed every 4-6 weeks by surgical team to assess need for adjustments to band volume

**Statistics**
- All tests two-sided, p values < 0.05
- Intent-to treat analysis
- χ² or t tests for baseline comparisons
- Multivariate analysis to assess weight and biochemical changes with time
- Logistic regression to examine association of diabetes remission
- Powered at 80% to detect 1% difference in A1c and 40% difference in diabetes remission

**Results**
- n=60
- **Baseline characteristics**
  - Age ≈ 47 y/o
  - A1c: 7.7%, BP: 136/85 mmHg, FBG: 157 mg/dL, TC: 200 mg/dL, TG: 189 mg/dL, HDL: 47 mg/dL
  - 13 patients with a BMI < 35 kg/m² (6 in surgical group and 7 in conventional group)
  - 39% hypertensive, 50% hypercholesterolemia, 47% hypertriglyceridemia
- **Loss to follow-up**
  - One surgical patient withdrew night before surgery
  - Three patients in conventional group withdrew within first month after randomization
  - One patient in conventional group withdrew at four months post randomization

<table>
<thead>
<tr>
<th>Outcome</th>
<th>LAGB (n=30)</th>
<th>Conventional (n=30)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes remission (%)</td>
<td>73</td>
<td>13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body weight reduction (kg)</td>
<td>-21</td>
<td>-1.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>A1c reduction (%)</td>
<td>-1.8</td>
<td>-0.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Outcome</td>
<td>LAGB (n=30)</td>
<td>Conventional (n=30)</td>
<td>P value</td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>-------------</td>
<td>---------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Fasting blood glucose reduction (mg/dL)</td>
<td>-51</td>
<td>-18</td>
<td>0.002</td>
</tr>
<tr>
<td>Total cholesterol reduction (mg/dL)</td>
<td>-3.6</td>
<td>-0.4</td>
<td>0.72</td>
</tr>
<tr>
<td>HDL increase (mg/dL)</td>
<td>+12.6</td>
<td>+2.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TG reduction (mg/dL)</td>
<td>-72</td>
<td>-2</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Baseline data carried forward for missing data in those loss to follow-up

- 80% one day hospital length of stay, longest stay of four days
- Seven patients in the conventional group used sibutramine at some time during the study
- Significance maintained when conservative analysis used assuming 4 noncompleters in conventional group achieved diabetes remission and 1 in surgical group did not (73% vs. 27%, p<0.001)
- Weight loss and lower baseline A1c independently associated with remission
- Baseline BMI, C-peptide did not predict remission
- Significant reduction in oral hypoglycemic (83%), antihypertensive (48%), lipid-lowering (28%) medications in surgical group
- Significant improvement in insulin resistance (~45%) in surgical group
- Adverse Events
  - No deaths
  - Four serious adverse events in surgical group (13%)
    - One patient developed port infection which resolved after two weeks of IV antibiotics
    - Two patients developed gastric pouch enlargement at 10 months post procedure, both underwent laparascopic procedure to replace gastric band
    - One patient developed persistent regurgitation, band removed at 15 days post procedure

**Authors’ Conclusions**
- Weight loss associated with LAGB results in diabetes remission in the majority of obese patients recently diagnosed with diabetes and was associated with greater improvements in features of the metabolic syndrome and use of related medications

**Strengths**
- Reported conservative analysis with those loss to follow-up
- First randomized controlled trial in bariatric surgery for remission of diabetes
- More stringent definition of remission compared to ADA definition

**Weaknesses**
- Single center with limited number of patients
- Recent, non-severe diagnosis of diabetes
- No report of insulin usage
- Conventional treatment did not receive T2D or GLP-1 analogs
- Short-term follow up of 2 years

**Purpose**
- To determine the remission rate of type 2 diabetes in patients receiving bariatric surgery

**Design**
- Single-center, nonblinded, randomized controlled trial

**Patient Population**
- **Inclusion:** 30-60 y/o, BMI ≥ 35 kg/m², T2DM ≥ 5 years duration, A1c ≥ 7.0%
- **Exclusion:** T1DM, diabetes secondary to specific disease or steroid therapy, previous bariatric surgery, pregnancy, other medical conditions requiring short-term hospitalization, severe diabetes complications, severe medical conditions

**Cohorts**
- **RYGB vs. biliopancreatic diversion vs. medical therapy**

**Outcomes**
- **Primary outcome:** rate of diabetes remission (FBG < 100 mg/dL or A1c < 6.5% for one year without medication)
- **Secondary outcomes:** changes in FBG, A1c, body weight, blood pressure, cholesterol, triglycerides

**Methods**
- Medical Therapy
  - Multidisciplinary visit with diabetologist, dietitian, nurse at baseline, 1, 3, 6, 9, 12, 24 months
  - Oral hypoglycemic and insulin optimized to goal A1c < 7%
  - Diet and lifestyle modification programs
- Bariatric Surgery
  - Multidisciplinary visit with diabetologist, dietitian, nurse at baseline, 1, 3, 6, 9, 12, 24 months
  - D/C of medical therapy considered as glycemic profile normalized
  - Daily MVI and mineral supplementation
  - Biliopancreatic group received extra vitamin D and calcium supplementation

**Statistics**
- Power of 90% to detect absolute difference of 65% in rate of remission between RYGB and medical therapy and 75% absolute difference between biliopancreatic diversion and medical therapy
- Not powered to detect differences between different surgeries
- Two sided p value = 0.025
- Intent-to-treat analysis
- One-way analysis of variance for continuous baseline characteristics
- $X^2$ for association between study group and rate of remission
- Kaplan-Meier procedure with log-rank test to compare surgical treatments for the time to remission
- Logistic regression for dependence of diabetes remission on some of the recorded variables

**Results**
- n=60
- Baseline characteristics:
  - Age ≈ 43 y/o, BMI ≈ 45 kg/m², diabetes duration ≈ 6 years, weight ≈ 134 kg
  - A1c ≈ 8.65%, blood pressure ≈ 151/95 mmHg
  - TC ≈ 237 mg/dL, LDL ≈ 154 mg/dL, HDL ≈ 38 mg/dL, TG ≈ 220 mg/dL
  - Significantly higher total cholesterol (237 vs. 182 mg/dL, p<0.005), LDL (154 vs. 109 mg/dL, p=0.008), and triglycerides (221 vs. 147 mg/dL, p=0.03) in medical therapy group vs. bariatric surgery

<table>
<thead>
<tr>
<th>Outcome</th>
<th>RYGB (n=20)</th>
<th>Diversion (n=20)</th>
<th>Medical (n=20)</th>
<th>p value RYGB vs. Diversion</th>
<th>p value Medical vs. Diversion</th>
<th>p value RYGB vs. Medical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes remission (%)</td>
<td>75</td>
<td>95</td>
<td>0</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>NR</td>
</tr>
<tr>
<td>Change in A1c (%)</td>
<td>-2.2</td>
<td>-3.9</td>
<td>-0.8</td>
<td>0.003</td>
<td>&lt;0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>Change in fasting blood glucose (mg/dL)</td>
<td>-70</td>
<td>-104</td>
<td>-38</td>
<td>0.005</td>
<td>&lt;0.001</td>
<td>0.03</td>
</tr>
<tr>
<td>Outcome</td>
<td>RYGB (n=20)</td>
<td>Diversion (n=20)</td>
<td>Medical (n=20)</td>
<td>p value Diversion vs. Medical</td>
<td>p value RYGB vs. Medical</td>
<td>p value RYGB vs. diversion</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>-------------</td>
<td>-----------------</td>
<td>----------------</td>
<td>-----------------------------</td>
<td>--------------------------</td>
<td>----------------------------</td>
</tr>
<tr>
<td>Change in body weight (% reduction)</td>
<td>-33</td>
<td>-34</td>
<td>-5</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>1.00</td>
</tr>
<tr>
<td>Total cholesterol reduction (mg/dL)</td>
<td>-17</td>
<td>-107</td>
<td>-47</td>
<td>0.31</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL reduction (mg/dL)</td>
<td>-25</td>
<td>-84</td>
<td>-39</td>
<td>1.00</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL increase (mg/dL)</td>
<td>+13</td>
<td>+4</td>
<td>+3</td>
<td>&lt;0.001</td>
<td>0.61</td>
<td>0.01</td>
</tr>
<tr>
<td>Triglyceride reduction (mg/dL)</td>
<td>-45</td>
<td>-135</td>
<td>-52</td>
<td>1.00</td>
<td>&lt;0.001</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*all outcomes at 2 years*

- Retention rate of 93% (56/60)
- Relative risk of diabetes remission
  - 7.5 in RYGB group (CI 1.97 to 28.6, p<0.001)
  - 9.5 in biliopancreatic diversion group (CI 2.54 to 35.51, p<0.001)
- Time to remission of diabetes significantly shorter in biliopancreatic group vs. RYGB group (4±1 months vs. 10±2 months in biliopancreatic group, p=0.01)
- Age, sex, baseline BMI, diabetes duration, and *weight change* not significant predictor of diabetes remission at 2 years
- Preoperative BMI did not predict remission of diabetes after either procedure
- Significant increase in HDL in RYGB vs. biliopancreatic diversion group (p<0.001)
- Antihypertensive medication reduced or discontinued in all patient groups (75% medical, 80% RYGB, 85% biliopancreatic diversion)
- Adverse Events
  - No deaths
  - Two serious adverse events in surgical groups (5%)
    - One patient required incisional hernia repair at 9 months post biliopancreatic diversion
    - One patient required reoperation for intestinal obstruction at 6 months post RYGB

**Authors’ Conclusions**

At two years, roux-en-Y gastric bypass and biliopancreatic diversion are far more effective than conventional medical therapy in the control of hyperglycemia in severely obese patients

**Strengths**

- Prospective, controlled groups
- Studied patients with long history of uncontrolled diabetes

**Weaknesses**

- Small sample size
- Significant baseline lipid differences between groups
- Short-term follow up
- Did not include patients with BMI 30-35 kg/m²
- No use of incretins

**Purpose**
- To compare the remission rate of type 2 diabetes in patients receiving intensive medical therapy and bariatric surgery

**Design**
- Single-center, nonblinded, randomized controlled trial

**Patient Population**
- Inclusion: 20-60 y/o, BMI 27 – 43 kg/m², A1c > 7%
- Exclusion: T1DM, previous bariatric surgery or complex abdominal surgery, poorly controlled medical or psychiatric disorders

**Cohorts**
- Bariatric surgery (RYGB) plus intensive medical therapy vs. sleeve gastrectomy plus intensive medical therapy alone

**Outcomes**
- **Primary outcome**: proportion of patients with A1C < 6% at one year with or without medication
- **Secondary outcomes**: changes in FBG, fasting insulin, A1c, CRP, body weight, blood pressure, lipids, insulin resistance (HOMA-IR), adverse events, medication changes

**Methods**
- **Intensive Therapy**
  - Diabetes specialist visit every 3 months for first year
  - Heavy use of new agents (GLP-1 analogs)
  - Goal A1c < 6%
  - Lifestyle counseling and weight management, encouraged to participate in Weight Watchers
  - All received lipid-lowering and antihypertensive medication with targets of BP < 130/80 mm Hg and LDL < 100 mg/dL
- **Bariatric Surgery**
  - Performed laparoscopically by a single surgeon
  - Multivitamin, iron, vitamin B12, calcium citrate plus vitamin D supplementation after RYGB
  - Multivitamin and vitamin B12 supplementation after sleeve gastrectomy

**Statistics**
- 150 patients (50 per group) provides power of 80% to detect absolute difference of 33% in achievement of A1c < 6% between RYGB + intensive therapy vs. sleeve gastrectomy + intensive medical therapy
- Power of 99% to detect any difference between surgical groups + intensive medical therapy vs. intensive medical therapy alone
- Two sided p value = 0.05
- Per-protocol analysis
- Analysis of variance for continuous laboratory measurements
- \(X^2\) for primary end point

**Results**
- n=140 (RYGB = 50, sleeve gastrectomy = 49, intensive therapy = 41)
  - 9 patients in intensive therapy group alone lost to follow-up
  - 1 patient in sleeve gastrectomy arm did not undergo procedure
- Baseline characteristics:
  - Age ≈ 48 y/o, BMI = 36 kg/m² (34% of patients had BMI < 35 kg/m²), Duration of diabetes ≈ 8 years
  - Baseline A1c = 9.2% (8.9% intensive alone, 9.3% RYGB + intensive, 9.5% gastrectomy + intensive)
  - 20% retinopathy, 28% micro or macroalbuminuria, 84% hyperlipidemic, 65% hypertensive
  - 86% on metformin, 41% on TZD, 44% on GLP-1 analog, 37% on secretagogue, 44% on insulin

<table>
<thead>
<tr>
<th>Outcome</th>
<th>RYGB + Intensive (n=50)</th>
<th>Gastrectomy + Intensive (n=49)</th>
<th>Intensive Therapy (n=41)</th>
<th>p value RYGB vs. Intensive</th>
<th>p value Gastrectomy vs. Intensive</th>
<th>p value RYGB vs. Gastrectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1c &lt; 6 %</td>
<td>42%</td>
<td>37%</td>
<td>12%</td>
<td>0.002</td>
<td>0.008</td>
<td>0.59</td>
</tr>
<tr>
<td>A1c &lt; 6 % w/ no meds</td>
<td>42%</td>
<td>27%</td>
<td>0%</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.10</td>
</tr>
<tr>
<td>A1c reduction (% change)</td>
<td>-2.9%</td>
<td>-2.9%</td>
<td>-1.4%</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.85</td>
</tr>
<tr>
<td>Outcome</td>
<td>RYGB + Intensive (n=50)</td>
<td>Gastrectomy + Intensive (n=49)</td>
<td>Intensive Therapy (n=41)</td>
<td>p value RYGB vs. Intensive</td>
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<td>p value RYGB vs. Gastrectomy</td>
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<td>---------------------------------</td>
</tr>
<tr>
<td>Change in body weight (kg)</td>
<td>-29</td>
<td>-25</td>
<td>-5</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.02</td>
</tr>
<tr>
<td>CRP reduction (% change)</td>
<td>-84</td>
<td>-80</td>
<td>-33</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.59</td>
</tr>
<tr>
<td>HDL increase (% change)</td>
<td>+28%</td>
<td>+28%</td>
<td>+11%</td>
<td>0.001</td>
<td>0.001</td>
<td>0.98</td>
</tr>
<tr>
<td>Triglyceride reduction (% change)</td>
<td>-44%</td>
<td>-42%</td>
<td>-14%</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.39</td>
</tr>
</tbody>
</table>

*all outcomes at one year

- Improvement in glycemic control seen by 3 months after surgical procedures
- Improvements in insulin resistance and hyperinsulinemia with bariatric surgery vs. intensive therapy
- Significant reduction in number of patients requiring lipid-lowering drugs at one year (27% RYGB and 39% gastrectomy vs. 92% intensive therapy, p<0.001)
- Significant reduction in diabetic medication use with bariatric procedures
  - **RYGB**: metformin (84% → 20%), TZD (50% → 0%), incretin (40% → 2%), secretagogue (34% → 2%), insulin (46% → 4%)
  - **Sleeve gastrectomy**: metformin (84% → 39%), TZD (35% → 10%), incretin (43% → 20%), secretagogue (37% → 10%), insulin (45% → 8%)
  - **Intensive**: metformin (93% → 97%), TZD (44% → 51%), incretin (49% → 87%), secretagogue (37% → 26%), insulin (51% → 38%)
- **Adverse Events**
  - No deaths
  - Serious events requiring hospitalization: 22% RYGB, 8% gastrectomy, 4% intensive
    - Reoperation in three patients post RYGB (blood clot evacuation, cholecystectomy, assessment of nausea/vomiting)
    - Reoperation in one patient post gastrectomy (jejunostomy due to gastric leak)

**Authors' Conclusions**

At one year, patients achieve glycemic control in significantly more patients with bariatric surgery plus intensive therapy compared to intensive therapy alone

**Strengths**

- Prospective, controlled groups
- Included patients of varying BMI
- Included patients with longest and most severe history of diabetes
- Most stringent definition of remission of all randomized controlled trials
- Used incretin therapy in comparator group

**Weaknesses**

- Small sample size
- Very short-term follow up
- No discussion of predictors of glycemic control post bariatric surgery
XVIII. Literature Review Summary
a. Bariatric procedures demonstrate diabetes remission at up to 2 years for obese patients with recent diabetes diagnosis up to 8 years after diagnosis
b. Remission is observed 3 to 9 months after surgical procedure
c. Due to short term follow-up of studies, durability of diabetes remission remains undetermined
d. No deaths reported, yet serious complications range from 5% to 22%, primarily due to reoperation
e. Predictors of Remission of T2DM
   i. RYGB > laparoscopic gastric banding
   ii. Controversy: diabetes remission independent of weight loss or preoperative BMI?
      1. Dixon: weight loss but not preoperative BMI predictive of remission
      2. Mingrone: weight loss and preoperative BMI not predictive of remission
      3. Schauer: did not comment on predictors or remission
      4. Verdict: more literature is needed to validate this claim

XIX. Bariatric Surgery Cost Effectiveness
a. Bariatric surgery cost effective at two years ($16,000 vs. $25,500 per diabetes case remitted)
b. RYGB cost-effective with $7,000/QALY in newly diagnosed patients with diabetes (< 5 years) and $12,000/QALY in established patients with diabetes (> 10 years)
c. Gastric banding cost-effective with $11,000/QALY in newly diagnosed patients with diabetes (< 5 years) and $13,000 in established patients with diabetes (> 10 years)

XX. Recommendations
a. Bariatric surgery in patients with type 2 diabetes
   i. Patients with severe or morbid obesity (BMI ≥ 35 kg/m²) and type 2 diabetes should be considered for bariatric surgery
   ii. Although a higher rate of diabetes remission has been associated with malabsorptive or mixed bariatric procedures, more long term head to head studies are needed before recommending a specific procedure in patients with type 2 diabetes
   iii. Use of laparoscopic procedures should be utilized to reduce the rate of complications
b. Areas for Research
   i. Long-term (>5 years) prospective randomized studies
   ii. Randomized studies in strictly class I obese patients with type 2 diabetes
   iii. Additional long-term (>5 year) cost effectiveness studies
   iv. Comparator studies powered to show difference between different procedures
   v. Replication of results at other sites
XXI. Sources


