The Role of Bariatric Surgery in Patients with Type-2 Diabetes (T2DM) and Cardiovascular Risk

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AACE California Chapter Meeting
18th Annual Meeting & Symposium
September 14-16, 2018
Disclosures

• Pharmaceutical support
  • None

• Off label medication use
  • None
Objectives

- Cite the bariatric surgery long-term glycemic outcomes in patients with T2DM
- Recognize the CVD risk factors improved by bariatric surgery
- Identify which patients with cardio-metabolic risk are most likely to benefit from bariatric surgery
Mechanistic Basis of CV Disease

- Myocardial Infarction
- Heart Failure
- Stroke
- Renal Failure
- Hypertension
- LDL-C
- Dyslipidemia
- Obesity
- CRP
- Age
- Diabetes
- IFG-IGT

Vascular Dysfunction → Vascular Disease
The Case for Bariatric Surgery
Management of T$_2$DM and CV risk co-morbidities

- **Obesity is a chronic disease** and should be treated to reduce morbidity and mortality
  - Obesity is present in **38%** of adults and **17%** of youth (NHANES 2013-14)$^1$

- **Behavioral changes** in diet and activity may be effective short-term, but often *not* long-term

- **Bariatric surgery** is very *effective* long-term
  - To ↓ **weight** and visceral adiposity
  - To ↓ **CV co-morbidity** of T$_2$DM, dyslipidemia, HTN
  - To ↓ **CVD morbidity and mortality**

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Projected Prevalence of T$_2$DM in the U.S. 1990 to 2050

Diabetes: 8.3% of the US population

Prevalence of T₂DM
Parallels obesity prevalence

**Obesity: NHANES Data**
U.S. Adults ≥20 Years

**Diabetes: CDC Data**
U.S. Population

BMI, body mass index (in kg/m²); CDC, Centers for Disease Control and Prevention; NHANES, National Health and Nutrition Examination Survey (x-axis lists last year of each survey). *NHANES 1994 data.

Excess Weight (BMI) and Disease Risk

- T2DM
- HTN
- GB Disease
- CHD

Willet WC et al. *NEJM* 1999;341:427

**Women**

**Men**

Relative Risk

BMI (kg/m²)

BMI (kg/m²)
Obesity and Risk of CVD Events
The HOPE Study: impact of abdominal adiposity

Adjusted Relative Risk

<table>
<thead>
<tr>
<th>Waist circumference (cm)</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tertile 1</td>
<td>&lt;95 cm</td>
<td>&lt;87 cm</td>
</tr>
<tr>
<td>Tertile 2</td>
<td>95–103 cm</td>
<td>87–98 cm</td>
</tr>
<tr>
<td>Tertile 3</td>
<td>&gt;103 cm</td>
<td>&gt;98 cm</td>
</tr>
</tbody>
</table>

Adjusted for BMI, age, smoking, sex, CVD, DM, HDL-cholesterol, total-C; CVD: cardiovascular disease; MI: myocardial infarction; BMI: body mass index; DM: diabetes mellitus; HDL: high-density lipoprotein cholesterol.

# NIH Weight Loss Therapy Guide

Based on BMI and comorbidity

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Body Mass Index (BMI, kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>25-26.9</td>
</tr>
<tr>
<td>Diet, Exercise, Behavior therapy</td>
<td>+</td>
</tr>
<tr>
<td>Pharmacotherapy</td>
<td>With Co-morbidity</td>
</tr>
<tr>
<td>Bariatric surgery</td>
<td>With DM CV Risk?</td>
</tr>
</tbody>
</table>

AACE Complication-Centric Model of Care

**STEP 1**
EVALUATION FOR COMPLICATIONS AND STAGING

- **CARDIOMETABOLIC DISEASE**
  - NO COMPLICATIONS
    - BMI 25–26.9, or BMI ≥ 27

- **BIOMECHANICAL COMPlications**
  - BMI ≥ 27 WITH COMPLICATIONS
    - Stage Severity of Complications
      - LOW
      - MEDIUM
      - HIGH
        - (i) Therapeutic targets for improvement in complications,
        - (ii) Treatment modality and
        - (iii) Treatment intensity for weight loss based on staging

**STEP 2**
SELECT:

- Lifestyle Modification:
- MD/RD counseling; web/remote program; structured multidisciplinary program

- Medical Therapy:
  - phentermine; orlistat; lorcaserin; phentermine/topiramate ER

- Surgical Therapy (BMI ≥ 35):
  - Lap band; gastric sleeve; gastric bypass

**STEP 3**
If therapeutic targets for improvements in complications not met, intensify lifestyle and/or medical and/or surgical treatment modalities for greater weight loss

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Medical Complications of Obesity

Obesity

Cardio-metabolic
- Dyslipidemia
- Hypertension
- Pre-diabetes (IFG, IGT)
- NAFLD
- PCOS
- Diabetes (T2DM)

Cardiovascular Disease

Biomechanical
- Osteoarthritis
- GERD
- Sleep apnea
- Pulmonary dysfunction
- Urine incontinence

Other
- Androgen deficiency
- Cancer
- Gallbladder disease
- Psychological disorders

GERD: gasto-esophageal reflux disease, IFG: impaired fasting glucose, IGT: impaired glucose tolerance, NAFLD: non-alcoholic fatty liver disease, PCOS: polycystic ovarian syndrome

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Current Bariatric Surgical Procedures

- Restrictive procedures
- Restrictive and malabsorptive procedures

- **Adjustable Gastric Band**
- **Vertical Sleeve Gastrectomy**
- **Roux-en-Y Gastric Bypass**
- **Biliopancreatic Diversion**

Bariatric Surgery 1-yr Weight Loss
ACS: Type of surgery and effect on weight loss (BMI)

ACS Bariatric Surgery Center Network Prospective Observational Study (n=28,616)

*P<0.05 vs baseline.

ACS, American College of Surgeons; BL, baseline; BMI, body mass index; LAGB, laparoscopic adjustable gastric band; LSG, laparoscopic sleeve gastrectomy; RYGB, Roux-en-Y gastric bypass.

Bariatric Surgery 7-yr Weight Loss
LABS: Longitudinal Assessment of Bariatric Surgery

<table>
<thead>
<tr>
<th>LABS¹</th>
<th>Laparoscopic Roux-en-Y Gastric Bypass (RYG)</th>
<th>Laparoscopic Adjustable Gastric Band (LAGB)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects</td>
<td>N=1738</td>
<td>N=610</td>
</tr>
<tr>
<td>Mean weight loss</td>
<td>28.4%</td>
<td>14.9%</td>
</tr>
<tr>
<td>Weight regain</td>
<td>3.9%</td>
<td>1.4%</td>
</tr>
<tr>
<td>Weight maintenance</td>
<td>75% maintained 20% wt loss</td>
<td>50% maintained 16% wt loss</td>
</tr>
<tr>
<td>Operative revisions</td>
<td>0.9 / 700 person yrs</td>
<td>30.3 / 700 person yrs</td>
</tr>
<tr>
<td>7-year death rate</td>
<td>3.7 / 700 person yrs</td>
<td>2.7 / 700 person yrs</td>
</tr>
</tbody>
</table>

• Improves **longevity** and may ↓ premature mortality 41%²
• Retrospective cohort (n=8385) lower **all-cause mortality** over 4.5 yrs follow up (HR: LAGB 2.01, LSG, 1.60, RYG 2.65) vs controls³
• Postop **GERD** worse with LSG vs RYG (32% vs 6.3%) and more **re-operative** interventions with RYG vs LSG (22% vs 16%), primarily internal hernias⁴

Bariatric Long-term Weight Loss

SOS: Surgery type and percent mean weight loss

Swedish Obese Subjects Study (n=4047)

RYGB 10-yr Outcomes

SOS: Effect on CV-related comorbidities

Bariatric 1-yr CVD Outcomes

ACS: Effect on CV-related comorbidities

American College of Surgeons (ACS) Bariatric Surgery Center Network Prospective Observational Study (N=28,616)

Patients with Resolution or Improvement (%)

<table>
<thead>
<tr>
<th>Condition</th>
<th>LAGB</th>
<th>LSG*</th>
<th>LRYGB</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2DM</td>
<td>44</td>
<td>55</td>
<td>83</td>
</tr>
<tr>
<td>HTN</td>
<td>44</td>
<td>68</td>
<td>79</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>33</td>
<td>35</td>
<td>66</td>
</tr>
</tbody>
</table>

*LSG with a small subject number with 1 year follow-up for all comorbidities (n≤38).

†P<0.05 vs LAGB
‡P<0.05 vs LRYGB

## RYGB 10-yr Outcomes

**Effect on CV and obesity-related comorbidities***

<table>
<thead>
<tr>
<th>Condition</th>
<th>Prevalence (%)</th>
<th>Improved (%)</th>
<th>Resolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma</td>
<td>10-15</td>
<td>100</td>
<td>&gt;95</td>
</tr>
<tr>
<td>Diabetes</td>
<td>15-20</td>
<td>100</td>
<td>90-95</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>15-25</td>
<td>85</td>
<td>70</td>
</tr>
<tr>
<td>Heart failure</td>
<td>10</td>
<td>90</td>
<td>60</td>
</tr>
<tr>
<td>Hypertension</td>
<td>30-60</td>
<td>90</td>
<td>60-65</td>
</tr>
</tbody>
</table>

**Resolved** = absence of symptoms, and no further need for treatment  
**Improved** = reduction of medication use

*Data compiled from >2000 patients in published series.*

Kral J. *Clin Perspect Gastroenterol* 2001
Bariatric Surgery 18-yr Mortality
SOS: CV mortality reduced in severely obese patients

Swedish Obese Subjects Study (n=4047)

Fatal CV Events
- Control (49 events)
- Surgery (28 events)
  HR, 0.56; 95% CI, 0.35-0.88;
  Log-rank $P = 0.01$

Total CV Events
- Control (49 events)
- Surgery (28 events)
  HR, 0.83; 95% CI, 0.69-1.00;
  Log-rank $P = 0.05$

BMI entry criteria: ≥34 kg/m² men, ≥38 kg/m² women. In post hoc analyses, a higher baseline insulin concentration was associated with a more favorable outcome of bariatric surgery on cardiovascular (CV) events. Sjostrom L. *JAMA.* 2012;307:56-65.
RYGB 5-yr Mortality
Canadian Series

89% ↓ in risk of death over 5 years
Relative Risk = 0.11 (.04-.27)

Bariatric Surgery
Mechanisms for weight loss

1st – Hormonal response
• Via direct delivery of food to the small intestine
• Increased GLP-1

2nd – Rapid negative caloric balance
• Glucose normalized within days
  • ↓ in hepatic lipid, as fat metabolized as a FFA fuel source
  • ↓ in hepatic glucose production, due to increased insulin sensitivity
• The predominant effect for T2DM control
Metabolic cross talk: BAs, GLP-1, FGF-19
# Bariatric Surgery

## Effect on appetite/satiety mechanisms

<table>
<thead>
<tr>
<th>Factor</th>
<th>Potential Post-surgery Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLP-1</td>
<td>↑ Increased satiety and decreased food intake.</td>
</tr>
<tr>
<td>GLP-2</td>
<td>↑ Mucosal cell mass response to injury:</td>
</tr>
<tr>
<td></td>
<td>• Increases in GLP-1 and PYY</td>
</tr>
<tr>
<td></td>
<td>• Gut proliferation, reducing malabsorption</td>
</tr>
<tr>
<td>GIP</td>
<td>↓ Reduced fat accumulation.</td>
</tr>
<tr>
<td>Ghrelin</td>
<td>↓ Reduced appetite.</td>
</tr>
<tr>
<td>Peptide-YY</td>
<td>↑ Increased satiety and decreased food intake.</td>
</tr>
<tr>
<td>Oxyntomodulin</td>
<td>↑ Increased satiety and decreased food intake.</td>
</tr>
<tr>
<td>Vagus denervation</td>
<td>Possible decreased hunger.</td>
</tr>
<tr>
<td>Altered gut flora</td>
<td>Shift in Bacteroides and Firmicutes gut bacteria to more like that present in lean individuals.</td>
</tr>
</tbody>
</table>

Metabolic Surgery and Glycemic Control

Potential mechanisms after RYGB and VSG

RYGB
- Caloric restriction
- Rapid emptying of nutrients into the small intestine
- Removal of the stomach fundus
- Exclusion of the duodenum and proximal jejunum from nutrients
- Enhanced nutrient/bile delivery to the mid/distal jejunum and ileum

SG

Altered bile acid / FGF-19 signalling
Altered microbiome
Altered gut hormones
Altered neural signalling
Intestinal adaptation / Reprogramming of intestinal glucose
Reduced hepatic and pancreatic triglycerides
Reduced glucotoxicity
Weight loss
Altered GI nutrient-sensing

Improved β-cell function / functional β-cell mass
Improved insulin sensitivity
Reduced hepatic glucose production
Increased glucose utilization
Increased glucose effectiveness

Diabetes Care
2016;39:893-901
IFG & T2DM: RYGB Long-term Outcomes
14-yr remission rates n 608 patients

Mean Weight △
(range, lbs)

• Preop 304 lbs (198-615)
• Yr-1 192 lbs (104-466)
• Yr-5 205 lbs (107-512)
• Yr-10 207 lbs (130-388)
• Yr-14 205 lbs (158-270)

(% normal FBG and HA1c after RYGB)

Patients with prior T2DM
82.9%
(121/146)

Patients with prior IFG
98.7%
(150/152)

SLEEVEPASS 5-yr Bariatric Surgery
RCT of SG vs RYG in patients with BMI>35

- **Subjects** – 240 adults (mean age 48, BMI 46 kg/m², 70% women) baseline T₂DM 42%, dyslipidemia 35%, HTN 71%

- **Randomized** – SG vs RYG; 80% completed 5-yr followup

- **Outcomes** – for weight loss and T₂DM remission
  - Mean % EWL 49% SG vs 57% RYG (8.2% Δ)
  - Complete T₂DM remission 5/41 (12%) SG and 10/40 (25%) RYG
    - Complete+partial remission 15/41 vs 18/40 (p>0.99)
    - Mean FBG 135 mg/dL SG and 121 mg/dL RYG (p=0.052)
    - A₁c 6.6% SG and 6.5% RYG (p=0.93)
  - **Drug Rx d/c’d** significant Δ SG vs RYG for HTN (29% vs 52%, p=0.02) and ns for dyslipidemia (47% vs 60%, p=0.15)

T2DM: Bariatric vs Medical Therapy: 1-yr

**Baseline:**
- n = 150 (93% completed 1-yr follow-up)
- 49.8 yo
- 66% women
- ave. A1c 9.2%
- BMI <35

**Primary endpoint:**
- A1c < 6.0% at 12 months

**BMI**
- Change in BMI over time
- P<0.001 for all groups

**FPG**
- Change in Fasting Plasma Glucose (mg/dl)
- P=0.02, P=0.001

**A1c**
- Change in Glycated Hemoglobin (percentage points)
- Schauer PR, et al. NEJM 2012;366:1567

**Rx’s**
- Average No. of Diabetes Medications
- P<0.001 for all groups

**Value at Visit**
- Intensive medical therapy
- Roux-en-Y gastric bypass
- Sleeve gastrectomy

**Value at Visit**
- Intensive medical therapy
- Roux-en-Y gastric bypass
- Sleeve gastrectomy

**Rx’s**
- Intensive medical therapy
- Roux-en-Y gastric bypass
- Sleeve gastrectomy
T₂DM: Bariatric vs Medical Therapy: 3-yrs

- **RCT** n=61, age 47, 82% F, 100.5 kg (43% with BMI<35), A1c 7.8%

- **Primary end points** were partial and complete T₂DM remission and **secondary** end points included T₂DM medications and weight change

- **Weight loss** with RYGB 25.0% (+2.0%), LAGB 15.0% (+2.0%) and lifestyle treatment 5.7% (+2.4%) (p < 0.01)

- **T2DM medication use** ↓ 65% after RYGB, ↓ 33% after LAGB, and 0% with intensive lifestyle intervention at 3-yrs (P < .001)

T₂DM: Bariatric Surgery & 5-yr Outcomes
Pre-operative BMI <35 kg/m²

66 patients with T₂DM and BMI 30 to 35 kg/m² at baseline

- 100% follow-up at 6-years
- High A1c pre-op despite all patients taking diabetes medication
- 88% of surgery patients off meds for T2DM at 5-yrs

T₂DM: RYGB with BMI<35
5-yr follow up

N=66, BMI 30-35
Initial A1c 9.7%

• 12.5 yrs T₂DM

Outcomes

• A1c: ↓ to 5.9%
• BP: ↓SBP, ↓DBP
• Lipids: ↓TC, ↓LDL, ↓TG, ↑HDL

Bariatric vs Medical Therapy in T2DM

11 RCTs reporting A1c in patients with 35<BMI>35

*In trials where more than one type of surgery was studied, each operation is displayed separately, compared with the medical/lifestyle group

Bariatric vs Medical Therapy in T2DM
Report of 11 RCTs

Baseline Compared to Final Post-operative HbA1c*

Bariatric vs Medical Therapy for T₂DM

5-year glycemic control in patients with 35<BMI>35

- **Baseline**: n=150, age 49±8 yrs, 66% women, mean BMI <37+3.5 kg/m² (range 27-43), mean A1c 9.2+1.5%.
- **Randomly assigned**: to (1) IMT alone or (2) IMT plus SG or RYGB.
- **Primary endpoint**: A1c ≤6.0% at 12 months (90% completed the 5-yr follow-up)

**Bariatric vs Medical Therapy for T\textsubscript{2}DM**

5-year glycemic control in patients with 35<BMI>35

- **Baseline:** n=150, age 49±8 yrs, 66% F, BMI <37+3.5 kg/m\textsuperscript{2} (range 27-43), A1c 9.2%
- **Primary endpoint:** A1c ≤6.0% at 12 months
  - Medical therapy 5% (n=2/38)
  - Sleeve gastrectomy 23% (n=11/47, p=0.07 adjusted, p=0.17 intention to treat analysis)
  - Gastric bypass 29% (n=14/49, p=0.03 adjusted, p=0.08 intention to treat analysis)

Bariatric Surgery vs Medical Therapy

RCT outcomes for both short and long-term glycemic control in patients with 35<BMI>35

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Ikramuddin 2013 (RYGB) [12 mo; ≤7.0%]</td>
<td>28</td>
<td>57</td>
<td>11</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>Ikramuddin 2015 (RYGBP) [24 mo; ≤7.0%]</td>
<td>26</td>
<td>60</td>
<td>8</td>
<td>59</td>
<td></td>
</tr>
<tr>
<td>Courcoulas 2014 (RYGB/LAGB) [12 mo; ≤6.5% off meds]</td>
<td>18</td>
<td>41</td>
<td>0</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Courcoulas 2015 (RYGB/LAGB) [36 mo; ≤6.5% off meds]</td>
<td>14</td>
<td>37</td>
<td>0</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Schauer 2012 (RYGB/SG) [12 mo; ≤6.0%]</td>
<td>34</td>
<td>99</td>
<td>0</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>Schauer 2014 (RYGB/SG) [36 mo; ≤6.0%]</td>
<td>27</td>
<td>97</td>
<td>0</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Mingrone 2012 (RYGBP/BPD) [24 mo; ≤6.5% off meds]</td>
<td>34</td>
<td>40</td>
<td>0</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Mingrone 2015 (RYGBP/BPD) [60 mo; ≤6.5% off meds]</td>
<td>19</td>
<td>38</td>
<td>0</td>
<td>15</td>
<td></td>
</tr>
</tbody>
</table>

**Fixed Effect Model**

- Data are arranged in order of ascending mean baseline BMI; the dotted line separates RCTs performed with cohorts exhibiting an ave. baseline BMI above or below 35 kg/m².
- Study duration and HbA₁c end point thresholds are shown in brackets; “off meds” indicates a threshold achieved off all T2DM meds; otherwise, end points represent HbA₁c thresholds achieved w/ or w/o meds.

The Case for Bariatric Surgery
For treatment of T\textsubscript{2}DM and CVD co-morbidities

• **Long-term goals** often *are met* following bariatric surgery vs behavior change\textsuperscript{1-3}, for:
  • treatment of T\textsubscript{2}DM
  • improving *cardio-metabolic* conditions
  • improved longevity
  • \(~0.5\) to 1\% perioperative 30 day mortality with experienced surgeons\textsuperscript{4-5}
  • 89\% ↓ mortality after RYGB at 5 yrs (Canada)
  • 24\% ↓ mortality for all bari-surgery at 10.9 yrs (SOS)

Thank You

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