Why Do We Treat Obesity?

Metabolic Complications
# Treatment Based on Clinical Judgment

## TREATMENT GOALS BASED ON DIAGNOSIS IN THE MEDICAL MANAGEMENT OF PATIENTS WITH OBESITY

<table>
<thead>
<tr>
<th>DIAGNOSIS</th>
<th>TREATMENT GOALS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anthropometric Component</strong></td>
<td><strong>Clinical Component</strong></td>
</tr>
<tr>
<td><strong>Clinical Component</strong></td>
<td><strong>Intervention/Weight-Loss Goal</strong></td>
</tr>
<tr>
<td><strong>Clinical Goals</strong></td>
<td></td>
</tr>
</tbody>
</table>

### TERTIARY PREVENTION

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Primary Diagnosis</th>
<th>Intervention Goal</th>
<th>Clinical Goals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overweight or Obesity</td>
<td>BMI ≥25 (≥23 in certain ethnicities)</td>
<td>Metabolic syndrome</td>
<td>10%</td>
</tr>
<tr>
<td>Prediabetes</td>
<td></td>
<td>10%</td>
<td>Prevention of T2D</td>
</tr>
</tbody>
</table>
| T2D                                            |                   | 5% to ≥15%        | • Reduction in A1C  
• Reduction in number and/or doses of glucose lowering medications  
• Diabetes remission especially when diabetes duration is short |
| Nonalcoholic fatty liver disease              | Steatosis          | 5% or more        | Reduction in intrahepatocellular lipid                                            |
| Steatohepatitis                               |                   | 10% to 40%        | Reduction in inflammation and fibrosis                                             |
Metabolic Complications of Obesity

Diabetes Risk
Criteria for Diagnosis of the Metabolic Syndrome

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cut Point</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waist circumference</td>
<td>Population or country-specific definitions</td>
</tr>
<tr>
<td></td>
<td>United States: Men: ≥102 cm (40.2 in)</td>
</tr>
<tr>
<td></td>
<td>Women: ≥88 cm (34.6 in)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>≥150 mg/dL or drug therapy* for hypertriglyceridemia</td>
</tr>
<tr>
<td>HDL-C</td>
<td>Men: &lt;40 mg/dL</td>
</tr>
<tr>
<td></td>
<td>Women: &lt;50 mg/dL</td>
</tr>
<tr>
<td></td>
<td>or drug therapy* for low HDL-C</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Systolic: ≥130 mmHg</td>
</tr>
<tr>
<td></td>
<td>Diastolic: ≥85 mmHg</td>
</tr>
<tr>
<td></td>
<td>or antihypertensive drug therapy/history of hypertension</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>≥100 mg/dL</td>
</tr>
<tr>
<td></td>
<td>or drug therapy for hyperglycemia</td>
</tr>
</tbody>
</table>

*Fibrates or nicotinic acid.

HDL-C = high-density lipoprotein cholesterol.
Metabolic Syndrome Is More Important Than Obesity in Terms of Cardiovascular Risk

Women's Ischemia Syndrome Evaluation (WISE) Study

3-Year Survival

Study Participants (%)

BMI (kg/m²)

80  85  90  95  100

≤24.9  25.0-29.9  ≥30  Overall

95.8  97.8  98.7  97.2

91.9  92.3  91.5

P=0.003

3-Year Risk of Death or MACE

HR (95% CI)  P value

Death
↑ BMI

0.92  (0.59-1.41)  0.69

0.95  (0.71-1.27)  0.73

Dysmetabolic

1.88  (1.38-2.57)  <0.0001

MACE

↑ BMI

2.01  (1.26-3.20)  0.003

*Metabolic syndrome or diabetes.

MACE = major adverse cardiac event (death, nonfatal myocardial infarction, stroke, congestive heart failure).

Risk of Developing T2D in Metabolically Healthy vs Unhealthy Individuals

Atherosclerosis Risk in Communities Study (N=14,685)

<table>
<thead>
<tr>
<th>Status</th>
<th>Healthy</th>
<th>1 or 2 Risk Factors*</th>
<th>Unhealthy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lean</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthy</td>
<td>0.47 (0.34-0.66)</td>
<td>1.07 (0.80-1.43)</td>
<td>2.33 (1.64-3.30)</td>
</tr>
<tr>
<td>Overweight</td>
<td>0.77 (0.56-1.08)</td>
<td>1.81 (1.36-2.41)</td>
<td>3.33 (2.46-4.51)</td>
</tr>
<tr>
<td>Obese</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthy</td>
<td>1 (reference)</td>
<td>2.84 (2.13-3.78)</td>
<td>5.42 (4.03-7.29)</td>
</tr>
</tbody>
</table>

*Untreated values: BP ≥130/85, fasting glucose ≥100 mg/dL, A1C ≥5.7%, TC ≥240, and/or HDL-C <40 in men or <50 in women.

BP = blood pressure; HDL-C = high density lipoprotein cholesterol; HR = hazard ratio; T2D = type 2 diabetes; TC = total cholesterol.

**Risk of CHD or Death in Metabolically Healthy vs Unhealthy**

**Atherosclerosis Risk in Communities Study (N=14,685)**

<table>
<thead>
<tr>
<th>Status</th>
<th>CHD HR (95% CI)</th>
<th>Mortality HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lean</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthy</td>
<td>0.92 (0.50-1.71)</td>
<td>0.97 (0.69-1.37)</td>
</tr>
<tr>
<td>1 or 2 risk factors*</td>
<td>2.26 (1.27-4.03)</td>
<td>1.39 (1.01-1.92)</td>
</tr>
<tr>
<td>Unhealthy</td>
<td>3.61 (1.96-6.66)</td>
<td>1.95 (1.37-2.78)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Status</th>
<th>CHD HR (95% CI)</th>
<th>Mortality HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overweight</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthy</td>
<td>0.95 (0.50-1.81)</td>
<td>0.90 (0.63-1.29)</td>
</tr>
<tr>
<td>1 or 2 risk factors*</td>
<td>2.48 (1.40-4.40)</td>
<td>1.33 (0.97-1.83)</td>
</tr>
<tr>
<td>Unhealthy</td>
<td>4.43 (2.48-7.92)</td>
<td>1.81 (1.30-2.53)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Status</th>
<th>CHD HR (95% CI)</th>
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<tbody>
<tr>
<td><strong>Obese</strong></td>
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<td></td>
</tr>
<tr>
<td>Healthy</td>
<td>1 (reference)</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>1 or 2 risk factors*</td>
<td>3.01 (1.69-5.35)</td>
<td>1.68 (1.22-2.32)</td>
</tr>
<tr>
<td>Unhealthy</td>
<td>5.47 (3.08-9.74)</td>
<td>2.52 (1.82-3.50)</td>
</tr>
</tbody>
</table>

*Untreated values: BP ≥130/85, fasting glucose ≥100 mg/dL, A1C ≥5.7%, TC ≥240, and/or HDL-C <40 in men or <50 in women.

BP = blood pressure; CHD = coronary heart disease; HDL-C = high density lipoprotein cholesterol; HR = hazard ratio; TC = total cholesterol.

Incidence Rates of Diabetes by Waist Circumference and Race/Ethnicity


Solid lines pertain to values between the race-specific 5th and 95th percentiles of waist circumference. Dotted lines are extrapolated values outside the aforementioned race-specific ranges. Adjusted for age, sex, education, and income.

10-Year Incidence of T2D as a Function of Increasing CMDS Risk Stage

CARDIA Study Cohort (N=3315)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No risk factors</td>
</tr>
</tbody>
</table>
| 1     | 1 or 2 risk factors  
Waist circumference, blood pressure, triglycerides, HDL-C |
| 2     | Metabolic syndrome or prediabetes  
Metabolic syndrome alone, or IFG, or IGT |
| 3     | Metabolic syndrome plus prediabetes  
2 or more out of 3: metabolic syndrome, IFG, IGT |
| 4     | End-stage cardiometabolic disease  
T2D and/or CVD |

CARDIA = Coronary Artery Risk Development in Young Adults; CMDS = cardiometabolic disease staging; CVD = cardiovascular disease; HDL-C = high density lipoprotein cholesterol; IFG = impaired fasting glucose; IGT = impaired glucose tolerance; T2D = type 2 diabetes.

Metabolic Complications of Obesity

Prevention of Diabetes: Lifestyle Studies
Self-Reported Risk Reduction Activities in Patients With Prediabetes

National Health and Nutrition Examination Survey

<table>
<thead>
<tr>
<th>Activity</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tried to lose or control weight</td>
<td>68%</td>
</tr>
<tr>
<td>Reduced dietary fat or calories</td>
<td>60%</td>
</tr>
<tr>
<td>Increased physical activity or exercise</td>
<td>55%</td>
</tr>
<tr>
<td>All 3</td>
<td>42%</td>
</tr>
</tbody>
</table>

Lifestyle Intervention in Prediabetes

- Persons with prediabetes should reduce weight by 5% to 10%, with long-term maintenance at this level
  - A program of regular moderate-intensity physical activity for 30-60 minutes daily, at least 5 days a week, is recommended
  - A diet that includes caloric restriction, increased fiber intake, and (in some cases) carbohydrate intake limitations is advised

## Prevention of T2D: Selected Lifestyle Modification Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>N</th>
<th>Baseline BMI (kg/m²)</th>
<th>Intervention period (years)</th>
<th>RRR (%)</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes Prevention Program</td>
<td>USA</td>
<td>3234</td>
<td>34.0</td>
<td>2.8</td>
<td>58</td>
<td>21</td>
</tr>
<tr>
<td>Diabetes Prevention Study</td>
<td>Finland</td>
<td>523</td>
<td>31</td>
<td>4</td>
<td>39</td>
<td>22</td>
</tr>
<tr>
<td>Da Qing</td>
<td>China</td>
<td>577</td>
<td>25.8</td>
<td>6</td>
<td>51</td>
<td>30</td>
</tr>
</tbody>
</table>

NNT = number needed to treat; RRR = relative risk reduction; T2D = type 2 diabetes.

Intensive Lifestyle Intervention Effectively Prevents Progression From IGT to T2D

Diabetes Prevention Program
(N=3234)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Diabetes Incidence per 100 Person-Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=1082)</td>
<td>11</td>
</tr>
<tr>
<td>Metformin 850mg BID (n=1073)</td>
<td>7.8</td>
</tr>
<tr>
<td>Intensive lifestyle intervention* (n=1079)</td>
<td>4.8</td>
</tr>
</tbody>
</table>

*Goal: 7% reduction in baseline body weight through low-calorie, low-fat diet and ≥150 min/week moderate intensity exercise.

IGT = impaired glucose tolerance; T2D = type 2 diabetes.

Lifestyle Intervention More Effectively Prevents Diabetes as Populations Age

Diabetes Prevention Program (N=3234)

Diabetes Incidence per 100 Person-Years

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Placebo</th>
<th>Metformin</th>
<th>Lifestyle</th>
</tr>
</thead>
<tbody>
<tr>
<td>25-44</td>
<td>11.6</td>
<td>6.7</td>
<td>6.2</td>
</tr>
<tr>
<td>45-59</td>
<td>10.8</td>
<td>7.6</td>
<td>4.7</td>
</tr>
<tr>
<td>≥60</td>
<td>10.8</td>
<td>9.6</td>
<td>3.1</td>
</tr>
</tbody>
</table>

*Goal: 7% reduction in baseline body weight through low-calorie, low-fat diet and ≥150 min/week moderate intensity exercise.

Effectiveness of Lifestyle Intervention for Diabetes Prevention Wanes as Weight Increases

Diabetes Prevention Program (N=3234)

<table>
<thead>
<tr>
<th>BMI (kg/m²)</th>
<th>Placebo</th>
<th>Metformin</th>
<th>Lifestyle</th>
</tr>
</thead>
<tbody>
<tr>
<td>22 to &lt;30</td>
<td>9</td>
<td>8.8</td>
<td>3.3</td>
</tr>
<tr>
<td>30 to &lt;35</td>
<td>8.9</td>
<td>7.6</td>
<td>3.7</td>
</tr>
<tr>
<td>≥35</td>
<td>14.3</td>
<td>7.0</td>
<td>7.3</td>
</tr>
</tbody>
</table>

Diabetes Incidence per 100 Person-Years

*Goal: 7% reduction in baseline body weight through low-calorie, low-fat diet and ≥150 min/week moderate intensity exercise.*

Maintenance of Long-Term Weight Loss

DPP Outcomes Study
(N=2766)

DPP = Diabetes Prevention Program; T2D = type 2 diabetes.

10-Year Incidence of T2D

DPP Outcomes Study
(N=2766)

DPP = Diabetes Prevention Program; T2D = type 2 diabetes.
Incidence of T2D

DPP Outcomes Study

- Intensive lifestyle intervention
- Metformin
- Placebo

DPP = Diabetes Prevention Program; DPPOS = Diabetes Prevention Program Outcomes Study; NS = not significant; T2D = type 2 diabetes.

Early Weight Loss Reduces Long-term Incidence of Type 2 Diabetes

Finnish Diabetes Prevention Study (N=522)

Follow-up Time (Years)

Kaplan-Meier estimate of probability of remaining free of diabetes

- Intervention
- Control

Log-rank test $P=0.0001$
Hazard ratio: 0.57 (95% CI 0.43-0.76)

Intensive lifestyle intervention goal: 5% reduction in body weight with moderate-intensity exercise for $\geq 30$ minutes/day plus diet consisting of $<30\%$ calories from fat, $<10\%$ calories from saturated fat, and $\geq 15$ mg fiber.

Cumulative Incidence of Diabetes Over 4 Years

The Finnish Diabetes Prevention Study

Cumulative Incidence of Diabetes in Asian Patients with IGT

**Da Qing Diabetes Prevention Study**

(N=577)

IGT = impaired glucose tolerance; T2D = type 2 diabetes.

20-Year Cumulative T2D Incidence in Asian Patients with IGT

Da Qing Diabetes Prevention Study

IGT = impaired glucose tolerance; T2D = type 2 diabetes.
23-Year Incidence of T2D in Asian Patients with IGT

**Da Qing Diabetes Prevention Study**

IGT = impaired glucose tolerance; T2D = type 2 diabetes.

Group Lifestyle Balance Program Intervention

- DPP lifestyle intervention adapted to a 12-session group-based program
- Implemented in a community setting in 2 phases using a nonrandomized prospective design
- Significant decreases in weight, waist circumference, and BMI noted in both phases vs baseline
- Average combined weight loss for both groups over the 3-month intervention: 7.4 pounds (3.5% relative loss, $P<0.001$)

DPP = Diabetes Prevention Program.
Translating the DPP Into Community Intervention

The DEPLOY Pilot Study
(N=92)

<table>
<thead>
<tr>
<th></th>
<th>Standard</th>
<th>DPP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δ Total Weight (%)</td>
<td>-2.0</td>
<td>-6.0</td>
</tr>
<tr>
<td></td>
<td>P&lt;0.001</td>
<td>P=0.008</td>
</tr>
<tr>
<td>Δ Total Cholesterol (mg/dL)</td>
<td>6.0</td>
<td>11.8</td>
</tr>
<tr>
<td></td>
<td>P&lt;0.001</td>
<td>P=0.002</td>
</tr>
</tbody>
</table>

4-6 months

12-14 months

DEPLOY = Diabetes Education & Prevention with a Lifestyle Intervention Offered at the YMCA; DPP = Diabetes Prevention Program; YMCA = Young Men's Christian Association.

Structured Programs Foster Adherence

Montana Diabetes Control Program
16-session program based on DPP-style intervention
(N=355)

DPP = Diabetes Prevention Program.
Metabolic Complications of Obesity

Prevention of Diabetes: Pharmacotherapy and Surgical Studies
Effect of Orlistat on Incidence of Diabetes in Obese Patients with Normal and Impaired Glucose Tolerance

XENDOS Study
(N=3305)

IGT Patients
- Placebo + lifestyle
- Orlistat + lifestyle

All Patients
- Placebo + lifestyle
- Orlistat + lifestyle

Cumulative Incidence of T2D

Weeks

IGT = impaired glucose tolerance; XENDOS = Xenical in the prevention of Diabetes in Obese Subjects.
Effect of Lorcaserin on Body Weight in Obese Adults Over 2 Years

BLOOM Study

Effect of Lorcaserin on Progression to T2D

Proportion of BLOOM and BLOSSOM Patients With Newly Diagnosed Diabetes After 52 Weeks of Treatment

T2D = type 2 diabetes.

Effect of Phentermine/Topiramate ER on Weight Loss in Obese Adults Over 2 Years

**SEQUEL Study**
(Completer Analysis)

Data are shown with mean (95% CI).

Phen/TPM ER = phentermine/topiramate extended release.

Effects of Phentermine/Topiramate ER on Glucose, Insulin, and Progression to T2D

**SEQUEL Study**  
(N=675)

**Glucose and Insulin**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Glucose (mg/dL)</th>
<th>Insulin (pmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting</td>
<td>-3.6, -5.4*</td>
<td>-18, -39, -37</td>
</tr>
<tr>
<td>2-h OGTT</td>
<td>-7.2, -10.8*, -18*</td>
<td>-157, -264*, -327*</td>
</tr>
</tbody>
</table>

**Annualized Incidence of T2D**

<table>
<thead>
<tr>
<th>Group</th>
<th>Progressors per year (%)</th>
<th>Annualized Incidence of T2D (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>3.7</td>
<td>54% P=NS</td>
</tr>
<tr>
<td>Phen/TPM CR 7.5/46 mg</td>
<td>1.7</td>
<td>76% P=0.008</td>
</tr>
<tr>
<td>Phen/TPM CR 15/92 mg</td>
<td>0.9</td>
<td></td>
</tr>
</tbody>
</table>

*P<0.005 vs placebo.

NS = not significant; Phen/TPM ER = phentermine/topiramate extended release; T2D = type 2 diabetes.

Effects of Phentermine/Topiramate ER in Patients at High Risk of Developing T2D

SEQUEL Prediabetes/Metabolic Syndrome Cohort (N=475)

*All groups had lifestyle intervention. NS = not significant; Phen/TPM ER = phentermine/topiramate extended release; T2D = type 2 diabetes.

Effect of Phentermine/Topiramate ER on Incidence of Diabetes

Phen/TPM ER = phentermine/topiramate extended release; T2D = type 2 diabetes.
Relationship Between Weight Loss and Prevention of Type 2 Diabetes

SEQUEL Prediabetes/Metabolic Syndrome Cohort (N=475)

ITT-LOCF Analysis

Annualized incidence rate of T2D

Magnitude of Weight Loss (%)

ITT = intent to treat; LOCF = last observation carried forward.

## Effect of Phentermine/Topiramate ER on Cardiometabolic Risk Markers

### CONQUER Study

<table>
<thead>
<tr>
<th>Risk Factors (Mean % Weight Loss)</th>
<th>Phentermine/Topiramate ER 7.5/46 mg (8.4%)</th>
<th>P value*</th>
<th>Phentermine/Topiramate ER 15/92 mg (10.4%)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP, mmHg</td>
<td>↓ -4.7</td>
<td>0.0008</td>
<td>↓ -5.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>↓ -3.4</td>
<td>NS</td>
<td>↓ -3.8</td>
<td>0.0031</td>
</tr>
<tr>
<td>Triglycerides, %</td>
<td>↓ -8.6</td>
<td>&lt;0.0001</td>
<td>↓ -10.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total cholesterol, %</td>
<td>↓ -4.9</td>
<td>0.0345</td>
<td>↓ -6.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LDL-C, %</td>
<td>↓ -3.7</td>
<td>NS</td>
<td>↓ -6.9</td>
<td>0.0069</td>
</tr>
<tr>
<td>HDL-C, %</td>
<td>↑ 5.2</td>
<td>&lt;0.0001</td>
<td>↑ 6.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>hsCRP, mg/L</td>
<td>↓ -2.49</td>
<td>&lt;0.0001</td>
<td>↓ -2.49</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Adiponectin, µg/mL</td>
<td>↑ 1.40</td>
<td>&lt;0.0001</td>
<td>↑ 2.08</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*P values represent comparisons to placebo.

Intent to treat, last observation carried forward analysis for total study population.

Effects of Liraglutide in Obese Patients with Prediabetes

**SCALE Obesity and Prediabetes (N=3731)**

**Weight Change After 56 Weeks**

**Patients with Prediabetes After 56 Weeks**

- **Liraglutide 3 mg**
  - Weight Change (Δ Weight): -8.4 kg
  - % Patients with Prediabetes: 20.7

- **Placebo**
  - Weight Change (Δ Weight): -2.8 kg
  - % Patients with Prediabetes: 30.8

*P<0.001 vs placebo.

Effects of Liraglutide in Obese Patients with Prediabetes

SCALE Obesity and Prediabetes
(N=3731)

Cumulative Incidence of Type 2 Diabetes

Effects of Liraglutide on Body Weight Over 3 Years

All arms included lifestyle intervention: −500 kcal/day hypocaloric diet + 150 min/week increased physical activity.

Full analysis set, fasting visit data only. Line graphs are observed means (±SE). Points (square, triangle) are observed means with last observation carried forward (LOCF).

Regression to Normoglycemia Among Patients with Prediabetes Treated With Liraglutide Over 3 Years

All arms included lifestyle intervention: ~500 kcal/day hypocaloric diet + 150 min./week increased physical activity.

Full analysis set. Statistical analysis is logistic regression.

CI = confidence interval; NNT = number needed to treat; OR = odds ratio.

Effect of Bariatric Surgery on Incidence of Type 2 Diabetes

Swedish Obesity Study

Hazard Ratio (95% CI)  
Control (392 events) 1.00 (ref) 
Surgery (110 events) 0.22 (0.18–0.27) 

P Value  
(ref) <0.001

Cumulative Incidence of Type 2 Diabetes

No. at Risk
Control 1771 1513 1076 404
Surgery 1658 1561 1225 576

Effect of Different Bariatric Surgeries on Weight-Related Comorbidities at 1 Year

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

*Small numbers of patients with 1 year of follow-up for all comorbidities (n≤38).

†P<0.05 vs LAGB; ‡P<0.05 vs LRYGB.

ACS = American College of Surgeons; BMI = body mass index; GERD = gastroesophageal reflux disease; LAGB = laparoscopic adjustable gastric band; LSG = laparoscopic sleeve gastrectomy; LRYGB = laparoscopic Roux-en-Y gastric bypass.

Metabolic Complications of Obesity

Type 2 Diabetes
Prevalence of CV Risk Factors in Diabetes

**Overweight / Obese**
- BMI <25 kg/m²: 12.9%
- BMI 25-<30 kg/m²: 25.9%
- BMI ≥30 kg/m²: 61.2%

**Hypertension**
- Normal: 29%
- BP ≥140/90 mmHg or taking antihypertensive medication: 71%

**Hyperlipidemia**
- Normal: 35%
- LDL-C ≥100 mg/dL or using cholesterol-lowering medication: 65%

BMI = body mass index.

Consequences of Obesity in Diabetes

- Increases risk of cardiovascular comorbidities
  - Hypertension
  - Dyslipidemia
  - Atherosclerosis
- May limit ability to engage in physical activity
- Increases insulin resistance
  - Worsens glucose tolerance
  - Necessitates higher exogenous insulin doses
- Changes neuroendocrine signaling and metabolism
- Reduces quality of life

Goal: 5% to 10% weight loss

## Weight Gain/Loss Potential with Antidiabetic Agents

<table>
<thead>
<tr>
<th>Class</th>
<th>Agent(s)</th>
<th>Weight Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amylin analogs</td>
<td>Pramlintide</td>
<td>↓</td>
</tr>
<tr>
<td>Biguanides</td>
<td>Metformin</td>
<td>↓</td>
</tr>
<tr>
<td>GLP-1 receptor agonists</td>
<td>Albiglutide, dulaglutide, exenatide, exenatide XR, liraglutide</td>
<td>↓↓</td>
</tr>
<tr>
<td>SGLT-2 inhibitors</td>
<td>Canagliflozin, dapagliflozin, empagliflozin</td>
<td>↓</td>
</tr>
<tr>
<td>α-Glucosidase inhibitors</td>
<td>Acarbose, miglitol</td>
<td>↔</td>
</tr>
<tr>
<td>Bile acid sequestrants</td>
<td>Colesevelam</td>
<td>↔</td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>Alogliptin, linagliptin, saxagliptin, sitagliptin</td>
<td>↔</td>
</tr>
<tr>
<td>Dopamine-2 agonists</td>
<td>Bromocriptine</td>
<td>↔</td>
</tr>
<tr>
<td>Glinides</td>
<td>Nateglinide, repaglinide</td>
<td>↑</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>Glimepiride, glipizide, glyburide</td>
<td>↑</td>
</tr>
<tr>
<td>Insulins</td>
<td>Aspart, degludec, detemir, glargine, glulisine, lispro, inhaled, NPH, regular</td>
<td>↑↑</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>Pioglitazone, rosiglitazone</td>
<td>↑↑</td>
</tr>
</tbody>
</table>

Metabolic Complications of Obesity

Effects of Lifestyle Change in Type 2 Diabetes
Intensive Intervention Reduces Significantly More Weight than Standard Approaches in T2D

Look AHEAD Trial
(N=5145)

- DSE = diabetes support and education; ILI = intensive lifestyle intervention; T2D = type 2 diabetes.
Long-term Limitations of Weight Loss Benefits in T2D

**Main effect:**
- Estimated mean A1C (%): -0.22 (95% CI -0.28 to -0.16)  
  *P*<0.001
- Estimated mean weight (kg): -4 (95% CI -5 to -3)  
  *P*<0.001

*P*<0.05 for between-group comparison.

Main effect is the average of post-baseline differences.

CI = confidence interval; T2D = type 2 diabetes.

Metabolic Complications of Obesity

Effects of Weight Loss Medications in Type 2 Diabetes
Effect of Phentermine/Topiramate ER on A1C and Number of Diabetes Medications

**SEQUEL Type 2 Diabetes Subgroup**

<table>
<thead>
<tr>
<th>Baseline Mean A1C (%)</th>
<th>Change in A1C</th>
<th>Change in Diabetes Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=55)</td>
<td>6.9</td>
<td>-0.04</td>
</tr>
<tr>
<td>Phen/TPM 7.5/46 mg (n=26)</td>
<td>7.3</td>
<td>1.9</td>
</tr>
<tr>
<td>Phen/TPM 15/92 mg (n=64)</td>
<td>6.9</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients With Net Change* in Concomitant Antihyperglycemics (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=227)</td>
</tr>
<tr>
<td>Phen/TPM 7.5/46 mg (n=153)</td>
</tr>
<tr>
<td>Phen/TPM 15/92 mg (n=295)</td>
</tr>
</tbody>
</table>

*Percent increase minus percent decrease. † The safety population was defined as all subjects who received at least 1 dose of study drug. ‡ P=0.013 for between-group differences.

LS = least squares; Phen/TPM = phentermine/topiramate.

Effects of Phentermine/Topiramate ER on Glucose Control in Advanced T2D

Poorly Controlled Type 2 Diabetes

Baseline Mean A1C (%)

<table>
<thead>
<tr>
<th>Placebo (n=55)</th>
<th>Phen/TPN 15/92 mg (n=75)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.6</td>
<td>8.8</td>
</tr>
</tbody>
</table>

Change in A1C

<table>
<thead>
<tr>
<th>Placebo (n=55)</th>
<th>Phen/TPN 15/92 mg (n=75)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-1.13</td>
<td>-1.61</td>
</tr>
</tbody>
</table>

Change in Diabetes Medications†

<table>
<thead>
<tr>
<th>Placebo (n=55)</th>
<th>Phen/TPN 15/92 mg (n=75)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>-16</td>
</tr>
</tbody>
</table>

*P=0.038 vs placebo.

LS = least squares; Phen/TPM = phentermine/topiramate; T2D = type 2 diabetes.

†Net score reflecting change in medication number and change in dose level of diabetes medications.

Effect of Lorcaserin on Glycemia in Type 2 Diabetes

**Baseline Mean A1C (%)**
- Placebo (n=248) 8.0
- Lorcaserin 10 mg BID (n=251) 8.1
- Lorcaserin 10 mg QD (n=93) 8.1

**Change in A1C**
- Placebo 0
- Lorcaserin 10 mg BID -0.9 *
- Lorcaserin 10 mg QD -1 *

**Change in Diabetes Medications**
- Placebo 88.3
- Lorcaserin 10 mg BID 82.9 †
- Lorcaserin 10 mg QD 76.6 †

**NNT = 4.4**
To achieve a 1.0% reduction in A1C

*P<0.001 vs placebo. †P=0.087 vs placebo.

BLOOM-DM = Behavioral Modification and Lorcaserin for Obesity and Overweight Management in Diabetes Mellitus.


Effect of Naltrexone/Bupropion SR on Glycemia in Type 2 Diabetes

COR = CONTRAVE Obesity Research; LOCF = last observation carried forward; MITT = modified intent to treat; SR, sustained release.

Effects of High- and Low-Dose Liraglutide in Type 2 Diabetes

SCALE Diabetes Study

<table>
<thead>
<tr>
<th>Baseline Mean A1C (%)</th>
<th>Placebo (n=212)</th>
<th>Liraglutide 1.8 mg (n=211)</th>
<th>Liraglutide 3 mg (n=423)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>7.9</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Change in A1C

- Placebo: -0.38
- Liraglutide 1.8 mg: -1.13
- Liraglutide 3 mg: -1.32

Change in Weight

- Placebo: -2
- Liraglutide 1.8 mg: -4.6
- Liraglutide 3 mg: -5.9

*P<0.0001 vs placebo.

Metabolic Complications of Obesity

Bariatric Surgery in Type 2 Diabetes
Surgical Intervention in Type 2 Diabetes

STAMPEDE Trial
(n=150)

FPG = fasting plasma glucose; STAMPEDE = Surgical Treatment and Medications Potentially Eradicate Diabetes Efficiently.

Resolution of Type 2 Diabetes After 3 Years

**STAMPEDE Trial**
(N=150 Patients with T2D at Baseline)

- **Medical T2D therapy** (n=40)
- **Sleeve gastrectomy** (n=49)
- **Gastric bypass** (n=48)

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*P<0.05, **P<0.01, ***P<0.001 vs medical therapy. †P=0.01 vs sleeve gastrectomy.

STAMPEDE = Surgical Treatment and Medications Potentially Eradicate Diabetes Efficiently; T2D = type 2 diabetes.

Loss of Glycemic Control After 3 Years

STAMPEDE Trial
(N=150 Patients with T2D at Baseline)

*Defined as failure to maintain A1C ≤6.0%.

**P=0.03 vs medical therapy.

T2D = type 2 diabetes.

Effect of Bariatric Surgery vs Medication plus Lifestyle Therapy on A1C in T2D

Second Diabetes Surgery Summit
(Systematic Review; N=11 RCTs)

Bariatric procedure
Follow-up (months)

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAGB</td>
<td>24</td>
</tr>
<tr>
<td>RYGB</td>
<td>12</td>
</tr>
<tr>
<td>Mult*</td>
<td>6</td>
</tr>
<tr>
<td>RYGB</td>
<td>12</td>
</tr>
<tr>
<td>Mult†</td>
<td>12</td>
</tr>
<tr>
<td>Mult‡</td>
<td>36</td>
</tr>
<tr>
<td>RYBG</td>
<td>12</td>
</tr>
<tr>
<td>LAGB</td>
<td>12</td>
</tr>
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</tr>
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<td>Mult§</td>
<td>12</td>
</tr>
<tr>
<td>RYGB</td>
<td>36</td>
</tr>
<tr>
<td>Mult§</td>
<td>12</td>
</tr>
<tr>
<td>RYGB</td>
<td>24</td>
</tr>
<tr>
<td>Mult§</td>
<td>60</td>
</tr>
</tbody>
</table>

ΔA1C (%)

Mean baseline BMI ≤35 kg/m²

Mean baseline BMI >35 kg/m²

*B RYGB, LAGB, or SG. † RYGB or LAGB. ‡ SYGB or SG. § RYGB or BPD.

BPD = biliopancreatic diversion; BMI = body mass index; LAGB = laparoscopic adjustable gastric band; Mult = multiple treatment arms; RCT = randomized controlled trial; RYGB = Roux en Y gastric bypass; SG = sleeve gastrectomy; T2D = type 2 diabetes.

Long-Term Diabetes Remission After Bariatric Surgery

Swedish Obese Subjects Study
(N=603 Patients with T2D at Baseline)

Prevalence of Diabetes Remission

Odds Ratio of Diabetes Remission

T2D = type 2 diabetes.
Metabolic Complications of Obesity

Liver Disease
Progression of NAFLD

CV = central vein; NAFLD = nonalcoholic fatty liver disease; NASH = nonalcoholic steatohepatitis; PT = portal triad; TG = triglyceride.

Effect of Weight Loss on NAFLD

Community Intervention Program
(N=154)

Intrahepatic Triglycerides
After 12 Months

Mean Δ IHTG (%)

-6.1

Lifestyle intervention
Mean WL: -5.6 kg

Control
Mean WL: -0.6 kg

-2.1

Patients Achieving NAFLD Remission*

Patients (%)

64

Lifestyle intervention
Mean WL: -5.6 kg

Control
Mean WL: -0.6 kg

20

*pAt month 12, defined as IHTG <5% by proton-magnetic resonance spectroscopy.

IHTG = intrahepatic triglyceride content; WL = weight loss.

Summary

- Obesity is associated with higher risks of prediabetes and type 2 diabetes
- Weight loss with lifestyle therapy, pharmacotherapy, or bariatric surgery
  - Reduces the risk of progression to type 2 diabetes
  - Improves glycemic control in patients with type 2 diabetes