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>Overweight or Obesity BMI ≥25</td>
<td>Metabolic syndrome</td>
</tr>
<tr>
<td>(≥23 in certain ethnicities)</td>
<td>Prediabetes</td>
</tr>
<tr>
<td></td>
<td>T2D</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nonalcoholic fatty liver disease</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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 (%)

- Normal
- Dysmetabolic*

P = 0.003

3-Year Risk of Death or MACE

<table>
<thead>
<tr>
<th></th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>0.92 (0.59-1.41)</td>
<td>0.69</td>
</tr>
<tr>
<td>Dysmetabolic</td>
<td>2.01 (1.26-3.20)</td>
<td>0.003</td>
</tr>
<tr>
<td>MACE</td>
<td>0.95 (0.71-1.27)</td>
<td>0.73</td>
</tr>
<tr>
<td></td>
<td>1.88 (1.38-2.57)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

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

### Lean
- Healthy: CHD HR (95% CI) 0.92 (0.50-1.71)
- 1 or 2 risk factors*: 2.26 (1.27-4.03)
- Unhealthy: 3.61 (1.96-6.66)

### Overweight
- Healthy: 0.95 (0.50-1.81)
- 1 or 2 risk factors*: 2.48 (1.40-4.40)
- Unhealthy: 4.43 (2.48-7.92)

### Obese
- Healthy: 1 (reference)
- 1 or 2 risk factors*: 3.01 (1.69-5.35)
- Unhealthy: 5.47 (3.08-9.74)

<table>
<thead>
<tr>
<th><strong>Risk Factor</strong></th>
<th><strong>CHD HR (95% CI)</strong></th>
<th><strong>Mortality HR (95% CI)</strong></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>
<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>
<tr>
<td><strong>Obese</strong></td>
<td></td>
<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)

- Stage 0: No risk factors
- Stage 1: 1 or 2 risk factors
  - Waist circumference, blood pressure, triglycerides, HDL-C
- Stage 2: Metabolic syndrome or prediabetes
  - Metabolic syndrome alone, or IFG, or IGT
- Stage 3: Metabolic syndrome plus prediabetes
  - 2 or more out of 3: metabolic syndrome, IFG, IGT
- Stage 4: End-stage cardiometabolic disease
  - T2D and/or CVD

Metabolic Complications of Obesity

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

National Health and Nutrition Examination Survey

- Tried to lose or control weight: 68%
- Reduced dietary fat or calories: 60%
- Increased physical activity or exercise: 55%
- All 3: 42%
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)

- Intensive lifestyle intervention* (n=1079)
  - Diabetes Incidence per 100 Person-Years: 4.8
- Metformin 850mg BID (n=1073)
  - Diabetes Incidence per 100 Person-Years: 7.8
- Placebo (n=1082)
  - Diabetes Incidence per 100 Person-Years: 11

*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)

*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 Incidence per 100 Person-Years

- **22 to <30 BMI (kg/m²)**: 9 (Placebo), 8.8 (Metformin), 3.3 (Lifestyle)
- **30 to <35 BMI (kg/m²)**: 8.9 (Placebo), 7.6 (Metformin), 3.7 (Lifestyle)
- **≥35 BMI (kg/m²)**: 14.3 (Placebo), 7.0 (Metformin), 7.3 (Lifestyle)

*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

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


Finnish Diabetes Prevention Study (N=522)

Follow-up Time (Years)

Kaplan-Meier estimate of probability of remaining free of diabetes

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

Intervention: 43%

Int 265 261 250 238 228 214 191 174 118
Con 257 251 231 209 192 176 157 140 91

No. at risk
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

University of Pittsburgh Primary Care Practice and Diabetes Prevention Support Center

- 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)

-2.0
-6.0
-1.8
-11.8
-30
-20
-10
0
20
-20
-10
0
10
20
-30
-21.6
-13.5

Δ Total Weight (%)

Δ Total Cholesterol (mg/dL)

4-6 months
12-14 months

P<0.001

P<0.001

P=0.008

P=0.002

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

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)

-45% decrease in T2D incidence for IGT patients (P=0.0024)
-37% decrease in T2D incidence for all patients (P=0.0032)

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

Study Week

Body Weight (kg)

Placebo in yr 1 and 2 (N=684)
Lorcaserin in yr 1, placebo in yr 2 (N=275)
Lorcaserin in yr 1 and 2 (N=564)

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

**CONQUER Trial**

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


**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></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>0</td>
<td>-18</td>
</tr>
<tr>
<td>Phen/TPM ER</td>
<td>-3.6</td>
<td>-39</td>
</tr>
<tr>
<td>Phen/TPM CR</td>
<td>-5.4 *</td>
<td>-37</td>
</tr>
<tr>
<td>2-h OGTT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>0</td>
<td>-18</td>
</tr>
<tr>
<td>Phen/TPM ER</td>
<td>-7.2 *</td>
<td>-39</td>
</tr>
<tr>
<td>Phen/TPM CR</td>
<td>-10.8 *</td>
<td>-37</td>
</tr>
</tbody>
</table>

**Annualized Incidence of T2D**

<table>
<thead>
<tr>
<th>Condition</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

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

<table>
<thead>
<tr>
<th></th>
<th>Liraglutide 3 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>-8.4 *</td>
<td>-2.8</td>
</tr>
</tbody>
</table>

*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

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

Likelihood of normoglycemia >3X higher with liraglutide 3 mg

OR = 3.6 (95% CI, 3.0 to 4.4); P<0.0001; NNT = ~3

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

- Control (392 events): Hazard Ratio (95% CI) - 1.00 (ref), P Value (ref) - <0.001
- Surgery (110 events): Hazard Ratio (95% CI) - 0.22 (0.18–0.27), P Value <0.001

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up yr</td>
<td>0000</td>
<td>0000</td>
</tr>
<tr>
<td>0</td>
<td>1771</td>
<td>1658</td>
</tr>
<tr>
<td>2</td>
<td>1513</td>
<td>1561</td>
</tr>
<tr>
<td>10</td>
<td>1076</td>
<td>1225</td>
</tr>
<tr>
<td>15</td>
<td>404</td>
<td>576</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Condition</th>
<th>LAGB</th>
<th>LSG*</th>
<th>LRYGB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>44</td>
<td>44</td>
<td>64</td>
</tr>
<tr>
<td>Hypertension</td>
<td>55</td>
<td>68</td>
<td>62</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td></td>
<td>33</td>
<td>66</td>
</tr>
<tr>
<td>Sleep apnea</td>
<td></td>
<td></td>
<td>62</td>
</tr>
<tr>
<td>GERD</td>
<td></td>
<td></td>
<td>64</td>
</tr>
</tbody>
</table>

*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%

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

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

**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)*

<table>
<thead>
<tr>
<th>Year</th>
<th>ILI Reduction</th>
<th>DSE Reduction</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year 1</td>
<td>-8.53</td>
<td>-0.63</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Year 2</td>
<td>-6.33</td>
<td>-0.92</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Year 3</td>
<td>-5.08</td>
<td>-0.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Year 4</td>
<td>-4.66</td>
<td>-1.06</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

DSE = diabetes support and education; ILI = intensive lifestyle intervention; T2D = type 2 diabetes.

Long-term Limitations of Weight Loss Benefits in T2D

Main effect: -4 (95% CI -5 to -3)
P<0.001

Main effect: -0.22 (95% CI -0.28 to -0.16)
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></th>
<th>Placebo</th>
<th>Phen/TPM 7.5/46 mg</th>
<th>Phen/TPM 15/92 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline Mean A1C (%)</strong></td>
<td>6.9</td>
<td>7.3</td>
<td>6.9</td>
</tr>
<tr>
<td><strong>Change in A1C</strong></td>
<td>-0.04</td>
<td>-0.42</td>
<td>-0.23</td>
</tr>
<tr>
<td><strong>Change in Diabetes Medications (Overall safety population†)</strong></td>
<td>7.1</td>
<td>1.9</td>
<td>0</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

Change in A1C

Placebo (n=55)
Baseline Mean A1C (%) 8.6

Phen/TPN 15/92 mg (n=75)
Change in A1C 8.8

Change in Diabetes Medications\(^\dagger\)

Placebo (n=55)
-1.13

Phen/TPN 15/92 mg (n=75)
-1.61 *

*P=0.038 vs placebo.

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

\(^\dagger\)Net score reflecting change in medication number and change in dose level of diabetes medications.

Effect of Lorcaserin on Glycemia in Type 2 Diabetes

BLOOM-DM Study

<table>
<thead>
<tr>
<th>Baseline Mean A1C (%)</th>
<th>Change in A1C</th>
<th>Placebo (n=248)</th>
<th>Lorcaserin 10 mg BID (n=251)</th>
<th>Lorcaserin 10 mg QD (n=93)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.0</td>
<td>-0.4</td>
<td>8.1</td>
<td>8.1</td>
<td></td>
</tr>
</tbody>
</table>

Patients Increasing Use of Antidiabetic Agents (%)

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=248)</th>
<th>Lorcaserin 10 mg BID (n=251)</th>
<th>Lorcaserin 10 mg QD (n=95)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>88.3</td>
<td>82.9</td>
<td>76.6</td>
</tr>
</tbody>
</table>

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-Diabetes Study

<table>
<thead>
<tr>
<th>Change in A1C</th>
<th>Change in Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=159)</td>
<td>Mean A1C (%) 8.0</td>
</tr>
<tr>
<td>Naltrexone/ bupropion SR (n=265)</td>
<td>Mean A1C (%) 8.0</td>
</tr>
<tr>
<td>-0.1</td>
<td>-0.6</td>
</tr>
</tbody>
</table>

Baseline Mean A1C (%)

-0.5 -1

Baseline Mean A1C (%)

-0.5 -1

P<0.001

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

**Change in A1C**

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean A1C (%)</th>
<th>LS Mean ΔA1C (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=212)</td>
<td>7.9</td>
<td>-0.38</td>
</tr>
<tr>
<td>Liraglutide 1.8 mg (n=211)</td>
<td></td>
<td>-1.13 *</td>
</tr>
<tr>
<td>Liraglutide 3 mg (n=423)</td>
<td></td>
<td>-1.32 *</td>
</tr>
</tbody>
</table>

**Change in Weight**

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean Weight (%)</th>
<th>LS Mean ΔWeight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=212)</td>
<td></td>
<td>-2</td>
</tr>
<tr>
<td>Liraglutide 1.8 mg (n=211)</td>
<td></td>
<td>-4.6 *</td>
</tr>
<tr>
<td>Liraglutide 3 mg (n=423)</td>
<td></td>
<td>-5.9 *</td>
</tr>
</tbody>
</table>

*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)

*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)

- Medical T2D therapy (n=5):
  - 80 patients

- Sleeve gastrectomy (n=18):
  - 50 patients

- Gastric bypass (n=21):
  - 24 patients

*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)

<table>
<thead>
<tr>
<th>Bariatric procedure</th>
<th>Follow-up (months)</th>
<th>Δ A1C (%)</th>
<th>Surgery</th>
<th>Medication+lifestyle</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAGB</td>
<td>24</td>
<td>-6</td>
<td>0</td>
<td>-6</td>
</tr>
<tr>
<td>RYGB</td>
<td>12</td>
<td>-5</td>
<td>0</td>
<td>-5</td>
</tr>
<tr>
<td>Mult*</td>
<td>6</td>
<td>-4</td>
<td>0</td>
<td>-4</td>
</tr>
<tr>
<td>RYGB</td>
<td>12</td>
<td>-3</td>
<td>0</td>
<td>-3</td>
</tr>
<tr>
<td>Mult†</td>
<td>12</td>
<td>-2</td>
<td>0</td>
<td>-2</td>
</tr>
<tr>
<td>Mult†</td>
<td>36</td>
<td>-1</td>
<td>0</td>
<td>-1</td>
</tr>
<tr>
<td>RYGB</td>
<td>12</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>LAGB</td>
<td>24</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>LAGB</td>
<td>12</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Mult‡</td>
<td>24</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Mult‡</td>
<td>12</td>
<td>4</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Mult‡</td>
<td>36</td>
<td>5</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>RYGB</td>
<td>12</td>
<td>6</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Mult$</td>
<td>24</td>
<td>7</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Mult§</td>
<td>60</td>
<td>8</td>
<td>0</td>
<td>8</td>
</tr>
</tbody>
</table>

-6 ≤35 kg/m²

Mean baseline BMI ≤35 kg/m²

Mean baseline BMI >35 kg/m²

*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
- Surgery
- Control

Follow-up Time
- 2 Years
- 10 Years
- 15 Years

Patients Without T2D (%)
- 2 Years: 72.3
- 10 Years: 38.1
- 15 Years: 30.4

Odds Ratio of Diabetes Remission
- 2 years: 13.3 (8.5-20.7)
- 10 years: 5.3 (2.9-9.8)
- 15 years: 6.3 (2.1-18.9)

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**

- **Lifestyle intervention**
  - Mean WL: -5.6 kg
  - Mean Δ IHTG: -6.1%
  - *P* < 0.001

- **Control**
  - Mean WL: -0.6 kg
  - Mean Δ IHTG: -2.1%

**Patients Achieving NAFLD Remission***

- **Lifestyle intervention**
  - Mean WL: -5.6 kg
  - Patients (%): 64

- **Control**
  - Mean WL: -0.6 kg
  - Patients (%): 20

*At 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