Prediabetes Management
AACE Prediabetes Consensus Statement: Summary

• Untreated individuals with prediabetes are at increased risk for diabetes as well as for micro- and macrovascular complications
• Treatment goals are to prevent deterioration in glucose levels and modify other risk factors such as obesity, hypertension, and dyslipidemia
  – The same blood pressure and lipid goals are suggested for prediabetes and diabetes
• Intensive lifestyle management is the cornerstone of all prevention efforts; pharmacotherapy targeted at glucose may be considered in high-risk patients

Prediabetes

• Epidemiologic evidence suggests that the complications of T2D begin early in the progression from NGT to frank diabetes

• Prediabetes and diabetes are conditions in which early detection is appropriate, because
  – Duration of hyperglycemia is a predictor of adverse outcomes
  – There are effective interventions to prevent disease progression and to reduce complications

NGT, normal glucose tolerance ; T2D, type 2 diabetes.
Policy Paradigm Shifts Needed to Stem Global Tide of T2D

• Integrating primary and secondary prevention along a clinical continuum
• Early detection of prediabetes and undiagnosed diabetes
• Implementing cost-effective prevention and control by integrating community and clinical expertise and resources within affordable service delivery systems
• Sharing and adopting evidence-based policies at the global level

T2D, type 2 diabetes.
# Lifestyle Therapy

## Risk Stratification for Diabetes Complications

### Intensity Stratified by Burden of Obesity and Related Complications

<table>
<thead>
<tr>
<th>Nutrition</th>
<th>Physical Activity</th>
<th>Sleep</th>
<th>Behavioral Support</th>
<th>Smoking Cessation</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Maintain optimal weight</td>
<td>• 150 min/week moderate exertion (e.g. walking, stair climbing)</td>
<td>• About 7 hours per night</td>
<td>• Community engagement</td>
<td>• No tobacco products</td>
</tr>
<tr>
<td>• Calorie restriction (if BMI is increased)</td>
<td>• Strength training</td>
<td>• Basic sleep hygiene</td>
<td>• Alcohol moderation</td>
<td></td>
</tr>
<tr>
<td>• Plant-based diet; high polyunsaturated and monounsaturated fatty acids</td>
<td>• Increase as tolerated</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Avoid <em>trans</em> fatty acids; limit saturated fatty acids</td>
<td>• Structured program</td>
<td></td>
<td>• Discuss mood with HCP</td>
<td>• Nicotine replacement therapy</td>
</tr>
<tr>
<td>• Structured counseling</td>
<td>• Wearable technologies</td>
<td></td>
<td></td>
<td>• Referral to structured program</td>
</tr>
<tr>
<td>• Meal replacement</td>
<td>• Medical evaluation/clearance</td>
<td></td>
<td>• Formal behavioral therapy</td>
<td></td>
</tr>
</tbody>
</table>

COPYRIGHT © 2018 AACE. MAY NOT BE REPRODUCED IN ANY FORM WITHOUT EXPRESS WRITTEN PERMISSION FROM AACE. DOI 10.4158/CS-2017-0153
**Prediabetes Algorithm**

**LIFESTYLE THERAPY**
(Including Medically Assisted Weight Loss)

- **TREAT ASCVD RISK FACTORS**
- **TREAT HYPERGLYCEMIA**
  - FPG > 100  |  2-hour PG > 140

**WEIGHT LOSS THERAPIES**

- **ASCVD RISK FACTOR MODIFICATIONS ALGORITHM**
  - **DYSLIPIDEMIA ROUTE**
  - **HYPERTENSION ROUTE**

**NORMAL GLYCEMIA**

- **PROGRESSION**

**OVERT DIABETES**

**PROCEDURE TO GLYCEMIC CONTROL ALGORITHM**

**LEGEND**

- Orlistat, lorcaserin, phentermine/topiramate ER, naltrexone/bupropion, liraglutide 3 mg, or bariatric surgery as indicated for obesity treatment

**1 PRE-DM CRITERION**

- **Intensify Weight Loss Therapies**
  - Metformin
  - Acarbose

**MULTIPLE PRE-DM CRITERIA**

- **Low-risk Medications**
  - Metformin
  - Acarbose
- **Consider with Caution**
  - TZD
  - GLP-1 RA

If glycemia not normalized
Feasibility of Preventing Type 2 Diabetes

• There is a long period of glucose intolerance that precedes the development of diabetes
• Screening tests can identify persons at high risk
• There are safe, potentially effective interventions that can address modifiable risk factors:
  – Obesity
  – Body fat distribution
  – Physical inactivity
  – High blood glucose

Interventions to Reduce Risks Associated With Prediabetes

• Therapeutic lifestyle management is the cornerstone of all prevention efforts

• No pharmacologic agents are currently approved for the management of prediabetes
  – Pharmacotherapy targeted at glucose may be considered in high-risk patients after individual risk-benefit analysis

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

Primary Care-Based Counseling for T2D Prevention: ADAPT

ADAPT System for Behavior-Change Counseling

Behavior-Change Principles
- Patient-selected behavior-change goals
- Behavior-change props
- Implementation-intentions exercise

Persuasive Psychology
- Behavior-change prescription
- Social comparisons
- Behavior-change samples
- Testimonials

Technology
- Electronic record–based goal-setting tool with facilitated order entry and documentation
- Website-based tailored reminders
- Frequent feedback about progress via email

ADAPT, Avoiding Diabetes Thru Action Plan Targeting; T2D, type 2 diabetes.
Self-Reported Risk Reduction Activities in Patients With Prediabetes

National Health and Nutrition Examination Survey

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

Prediabetes Management

PREVENTION OF DIABETES: LIFESTYLE STUDIES
## Prevention of T2D: Selected Lifestyle Modification Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>N</th>
<th>Baseline BMI (kg/m(^2))</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): 4.8 (58%)
- Metformin 850mg BID (n=1073): 7.8 (31%)
- Placebo (n=1082): 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 Prevention Program (N=3234)

*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.

10-Year Incidence of Type 2 Diabetes

DPP Outcomes Study

DPP, Diabetes Prevention Program; DPPOS, Diabetes Prevention Program Outcomes Study; T2D, type 2 diabetes.

T2D Prevention in Women With a History of GDM

• Findings from the DPP
  – Progression to diabetes is more common in women with a history of GDM vs those without, despite equivalent degrees of IGT at baseline

• Both intensive lifestyle and metformin are highly effective in delaying or preventing diabetes in women with IGT and a history of GDM

DPP, Diabetes Prevention Program; GDM, gestational diabetes mellitus; IGT, impaired glucose tolerance; T2D, type 2 diabetes.
Effect of Lifestyle Modification on Weight and Blood Pressure

The Finnish Diabetes Prevention Study

- Weight (kg)
- Waist (cm)
- SBP (mm Hg)
- DBP (mm Hg)

Control (n=250) vs. Diet intervention (n=256)

Change from baseline

- Weight (kg): $P<0.001$
- Waist (cm): $P<0.001$
- SBP (mm Hg): $P=0.007$
- DBP (mm Hg): $P=0.02$

DBP, diastolic blood pressure; SBP, systolic blood pressure.
Effect of Lifestyle Modification on Glucose in Patients with IGT

The Finnish Diabetes Prevention Study

IGT, impaired glucose tolerance.
Cumulative Incidence of Diabetes Over 4 Years

The Finnish Diabetes Prevention Study

Control (n=250)  Diet intervention (n=256)

78%下降到32%

DBP, diastolic blood pressure; SBP, systolic blood pressure.

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 All-Cause Mortality in Asian Patients with IGT

Da Qing Diabetes Prevention Study

IGT, impaired glucose tolerance.
23-Year Cardiovascular Mortality in Asian Patients with IGT

Da Qing Diabetes Prevention Study

IGT, impaired glucose tolerance.
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)

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.
Prediabetes Management

PREVENTION OF DIABETES: PHARMACOTHERAPY AND SURGICAL STUDIES
## Medical and Surgical Interventions Shown to Delay or Prevent T2D

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Follow-up Period</th>
<th>Reduction in Risk of T2D (P value vs placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antihyperglycemic agents</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metformin(^1)</td>
<td>2.8 years</td>
<td>31% (P&lt;0.001)</td>
</tr>
<tr>
<td>Acarbose(^2)</td>
<td>3.3 years</td>
<td>25% (P=0.0015)</td>
</tr>
<tr>
<td>Pioglitazone(^3)</td>
<td>2.4 years</td>
<td>72% (P&lt;0.001)</td>
</tr>
<tr>
<td>Rosiglitazone(^4)</td>
<td>3.0 years</td>
<td>60% (P&lt;0.0001)</td>
</tr>
<tr>
<td><strong>Weight loss interventions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orlistat(^5)</td>
<td>4 years</td>
<td>37% (P=0.0032)</td>
</tr>
<tr>
<td>Phentermine/topiramate(^6)</td>
<td>2 years</td>
<td>79% (P&lt;0.05)</td>
</tr>
<tr>
<td>Bariatric surgery(^7)</td>
<td>10 years</td>
<td>75% (P&lt;0.001)</td>
</tr>
</tbody>
</table>

T2D, type 2 diabetes.

The Effect of Metformin on the Progression of IGT to Diabetes Mellitus

The Chinese Prevention Study (N=321)

IGT, impaired glucose tolerance; RRR, relative risk reduction.

Effect of Lifestyle Modification and Metformin on Cumulative Diabetes Incidence

The Indian DPP (N=531)

DPP, Diabetes Prevention Program; LSM, lifestyle modification; MET, metformin; RRR, relative risk reduction.

Effect of Acarbose on Reversion of IGT to NGT

STOP-NIDDM

Placebo (n=715) 30.9

Acarbose (n=714) 35.3

P<0.0001

IGT, impaired glucose tolerance; NGT, normal glucose tolerance; STOP-NIDDM, Study to Prevent Non-Insulin Dependent Diabetes Mellitus.

DREAM, Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication.

Effect of Pioglitazone on Development of T2D in Patients with IGT

ACT NOW, Actos Now for the Prevention of Diabetes; IGT, impaired glucose tolerance; T2D, type 2 diabetes.

Special Considerations for Thiazolidinedione Use in Patients With Prediabetes

• Because of the known adverse effects of the TZDs, these agents should be considered only for patients at the greatest risk of developing future diabetes and those failing more conventional therapies.
Effects of Exenatide and Lifestyle Modification on Body Weight and Glucose Tolerance in Obese Patients With and Without Prediabetes

- **Patients**
  - N=152, weight 108.6 +/- 23.0 kg, BMI 39.6 +/- 7.0 kg/m² (IGT or IFG 25%)

- **Design**
  - 24-week randomized controlled trial: exenatide or placebo plus lifestyle intervention

- **Results:**
  - Exenatide-treated patients lost 5.1 kg from baseline vs 1.6 kg with placebo (P<0.001)
  - Both groups reduced their daily caloric intake
  - IGT or IFG normalized at end point in 77% and 56% of exenatide and placebo subjects, respectively

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

Patients with A1C ≥6.5% (%)

- Placebo
- Lorcaserin

P=0.003

T2D, type 2 diabetes.

## Effect of Lorcaserin on Cardiometabolic Risk Markers

### BLOOM Study

<table>
<thead>
<tr>
<th>Risk Factors (Mean % Weight Loss)</th>
<th>Lorcaserin 10 mg (5.8%)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP, mmHg</td>
<td>↓  -1.4</td>
<td>0.04</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>↓  -1.1</td>
<td>0.01</td>
</tr>
<tr>
<td>Triglycerides, %</td>
<td>↓  -6.15</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total cholesterol, %</td>
<td>↓  -0.90</td>
<td>0.001</td>
</tr>
<tr>
<td>LDL-C, %</td>
<td>↑  2.87</td>
<td>0.049</td>
</tr>
<tr>
<td>HDL-C, %</td>
<td>↑  0.05</td>
<td>NS</td>
</tr>
<tr>
<td>hsCRP, mg/L</td>
<td>↓  -1.19</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fibrinogen, mg/dL</td>
<td>↓  -21.5</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*P values represent comparisons to placebo.

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

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>Treatment</th>
<th>Fasting Glucose (mg/dL)</th>
<th>2-h OGTT Glucose (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>-18</td>
<td>-157</td>
</tr>
<tr>
<td>Phen/TPM CR 7.5/46 mg</td>
<td>-39</td>
<td>-264</td>
</tr>
<tr>
<td>Phen/TPM CR 15/92 mg</td>
<td>-37</td>
<td>-327</td>
</tr>
</tbody>
</table>

**Annualized Incidence of T2D**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Progressors per year (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>3.7</td>
</tr>
<tr>
<td>Phen/TPM CR 7.5/46 mg</td>
<td>1.7</td>
</tr>
<tr>
<td>Phen/TPM CR 15/92 mg</td>
<td>0.9</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.

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 (%)
# 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

SCALE Obesity (N=3731)

Weight Change After 56 Weeks

<table>
<thead>
<tr>
<th>Δ Weight (%)</th>
<th>Liraglutide (n=2437)</th>
<th>Placebo (n=1225)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-16</td>
<td>-8</td>
<td>-2.6</td>
</tr>
</tbody>
</table>

P<0.001

Effects of Liraglutide in Obese Patients with Prediabetes

SCALE Obesity and Prediabetes (N=3731)

Weight Change After 56 Weeks

- Liraglutide 3 mg
- Placebo

Patients with Prediabetes After 56 Weeks

*P<0.001 vs placebo.

Effect of Bariatric Surgery on Incidence of Type 2 Diabetes

Swedish Obesity Study

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

Patients with resolution or improvement of condition (%)

Diabetes: LAGB 44, LSG 55, LRYGB 83
Hypertension: LAGB 44, LSG 68, LRYGB 79
Hyperlipidemia: LAGB 33, LSG 35, LRYGB 66
Sleep apnea: LAGB 38, LSG 62, LRYGB 66
GERD: LAGB 64, LSG 50, LRYGB 70

*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.