Treating Patients with Obesity Using the AACE Comprehensive Clinical Practice Guidelines

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Disclosures

► Consulting Fees/Advisory Boards:

   Merck, Astra Zeneca, Eisai, Janssen, Novo Nordisk, Vivus, Takeda, Alexion

► Research:

   Merck, Novo Nordisk, Pfizer, Sanofi, Eisai, Astra Zeneca, Lexicon, Weight Watchers, Elcelyx
1. "It is the strong contention of AACE that the view of obesity as a behavioral decision is debunked by biomedical evidence."

2. "…obesity is a primary disease, and the full force of our medical knowledge should be brought to bear on the prevention and treatment of obesity as a primary disease entity."

3. "…obesity is an altered physiological and metabolic state, with genetic, environmental, and behavioral determinants, which results in increased morbidity and mortality."

Determinants of Body Weight

**Genes**
- Protective and at risk alleles for weight gain
- Race (ancestral admixture)
- Gene-Gene interactions

**Environment**
- Food availability
- Food quality
- Built environment
- Socioeconomic status
- Education

**Biological factors**
- In utero environment
- Birth Weight
- Gender
- Age
- Concurrent diseases

**Behavior**
- Dietary preferences
- Physical activity
- Psychological factors
- Cultural factors
- Diurnal life patterns
BMI Increases as the Number of Susceptibility Alleles Increases

Cause of Obesity: Abnormal Energy Balance

Body Weight

Increase

Energy intake
Ingestion of:
Proteins
Fats
Carbohydrates

Human being: biological and behavioral interface

Decrease

Energy expenditure
Basal metabolic rate
Physical activity
Energy to metabolized food

Garvey WT, 2012
AMA: Essential Criteria of a Disease

1. Characteristic signs or symptoms
2. Impairment in the normal functioning of some aspect of the body
3. Results in harm or morbidity
**Assessing Weight: BMI and Waist Circumference**

<table>
<thead>
<tr>
<th>Weight Category</th>
<th>BMI Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal weight</td>
<td>BMI 18.5-24.9</td>
</tr>
<tr>
<td>Overweight</td>
<td>BMI 25.0-29.9</td>
</tr>
<tr>
<td>Obesity class 1</td>
<td>BMI 30.0-34.9</td>
</tr>
<tr>
<td>Obesity class 2</td>
<td>BMI 35.0-39.9</td>
</tr>
<tr>
<td>Obesity class 3 (extreme/morbid)</td>
<td>BMI ≥40.0</td>
</tr>
</tbody>
</table>

*World Health Organization defines overweight as BMI ≥25 kg/m² and obese as BMI ≥30 kg/m².*

Regulation of Energy Intake

Peripheral Signals

- GHRELIN
- LEPTIN
- CCK
- GLP-1
- PEPTIDE YY
- AMYLIN
- INSULIN

Hypothalamic Pathways

- Arcuate Nucleus
  - NPY AgRP
  - GSHR
- PVN, LHA, DMN
  - NPY
  - Y1R
  - Y5R

Anorexigenic Pathway

- POMC/CART
  - αMSH
  - Y2R
  - GLPR1
  - 5HT2c
  - μ-OR
  - MC4R

Orexigenic Pathway

- BDNF
  - NTRK2
  - MCH1R
  - MCH
  - MCH1R

Higher Cortical Centers

Garvey WT, 2013.
In Obesity, biology protects against weight loss and maintains a high body weight

- **↑** Ghrelin
- **↓** Leptin, PYY, CCK, Amylin
- **↓** Resting energy expenditure
- **↑** Hunger
- **↑** Calorie-dense food preferences

**Baseline weight**
250 lbs

**Equilibrium Weight**

**Weight Loss**

**Weight Gain**

Garvey WT, 2014
In Obesity, fat tissue can be inflamed (i.e., “sick fat”) and function abnormally.
Increased fat mass → Increased cell size/pathology

- Osteoarthritis
- Sleep Apnea
- Stigma
- Urinary Incontinence

Excess fat storage

Environment → ↓ Energy Expenditure
Genetics → ↑ Energy Intake

Energy Intake

- Poor Quality of Life
- Impaired Function
- Morbidity & Mortality
- Disease

Metabolic Syndrome
- Diabetes
- Pre-diabetes
- NAFLD
- Cancer
- HTN
- CVD

The Spectrum of Cardiometabolic Disease

Prediabetic States
1. Prediabetes
   i. IFG
   ii. IGT
2. Metabolic Syndrome
   • Waist
   • Blood pressure
   • Fasting glucose
   • Triglycerides
   • HDL-cholesterol

Type 2 Diabetes

Cardiovascular Disease

Insulin Resistance

Obesity

IFG, impaired fasting glucose; IGT, impaired glucose tolerance

Garvey WT, 2013
Treatment Modalities for Patients with Overweight and Obesity

Treatment of Obesity
- Lifestyle Intervention
- Medications
- Bariatric Surgery
## Comprehensive Lifestyle Management

**Is the Foundation of Obesity Treatment**

### Meal Plan
- Reduced-calorie healthy meal plan
- ≈ 500-750 kcal daily deficit
- Many healthy meal plan options
- Meal replacements
- Very-low–calorie diet is an option for selected patients—requires supervision

**Team member/expertise:** dietitian, health educator

### Physical Activity
- Aerobic activity
  - Goal: > 150 min/wk
  - 3-5 days/wk
- Resistance exercise
  - Major muscle groups
  - 2-3 times/wk
- Reduce sedentary behavior
- Individualized (e.g., preferences, limitations)

**Team member/expertise:** exercise trainer, physical activity coach, physical/occupational therapist

### Behavior
- Intervenational package of behavioral methods
- Self-monitoring; goal setting; education; problem-solving; stimulus control; stress reduction; psychological evaluation and treatment; cognitive restructuring; motivational interviewing; social support structures

**Team member/expertise:** health educator, behaviorist, clinical psychologist, psychiatrist

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*a AACE/ACE guideline lists: Mediterranean, DASH, low-carb, low-fat, volumetric, high protein, vegetarian.

Intensification of Lifestyle Therapies to Achieve Weight Loss Goals

**Lifestyle Therapy**

- Simple advice to lose weight in doctor’s office
- Internet programs or self-help books
- Advice from dietitian
- Structured programs (Weight Watchers, YMCA, telecommunication)
- Multidisciplinary structured programs
- Physician-driven individualized structured programs

Impart skills and behavior change to induce and maintain weight loss
Remember the Pathophysiology of Obesity: mechanisms protecting against weight loss.

It is difficult for patients to maintain their weight loss over time.

Sacks FS. et al. *NEJM* 2009;360(9) 859-873.
## Obesity Pharmacotherapy

<table>
<thead>
<tr>
<th>Agents</th>
<th>Action</th>
<th>Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Previously available</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phentermine</td>
<td>• Sympathomimetic</td>
<td>• 1959</td>
</tr>
<tr>
<td>Orlistat</td>
<td>• GI lipase inhibitor</td>
<td>• 1997</td>
</tr>
<tr>
<td><strong>Recently Approved</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phentermine/Topiramate ER</td>
<td>• Sympathomimetic/Anticonvulsant (GABA receptor modulation?)</td>
<td>• Approved, Summer 2012</td>
</tr>
<tr>
<td>Lorcaserin</td>
<td>• 5-HT&lt;sub&gt;2C&lt;/sub&gt; serotonin receptor agonist</td>
<td>• Approved, Summer 2012</td>
</tr>
<tr>
<td>Naltrexone ER/Bupropion ER</td>
<td>• Dopamine/noradrenaline reuptake inhibitor/Opioid receptor antagonist</td>
<td>• Approved, September 2014</td>
</tr>
<tr>
<td>Liraglutide 3 mg</td>
<td>• GLP-1 receptor agonist</td>
<td>• Approved December 2014</td>
</tr>
</tbody>
</table>

US FDA. Drugs@FDA. http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA.
Principles for Use of Weight Loss Medications

• Use as an adjunct to a lifestyle intervention program.
• Addition of a weight-loss medication consistently achieves greater weight loss than that achieved by the lifestyle intervention alone, and helps sustain weight loss for a longer period of time.
• Presence of obesity-related complications and need for more aggressive weight loss therapy.
• Obesity is a life-long disease and requires long-term treatment and follow-up.
• FDA “off-ramp”
• The ASBP, AACE and AHA/ACC/TOS Obesity Guidelines all advise use of medications for patients who have sufficient health risk, not for cosmetic reasons.
Effect of Phentermine/Topiramate ER on Weight Loss in Obese Adults Over 2 Years: SEQUEL Study

Individuals With Obesity Lose More Weight With Agents Approved for Long-Term Use vs Placebo

Median Rate of Categorical Weight Loss, % of participants

- Placebo
- Orlistat
- Lorcaserin
- Naltrexone ER/bupropion ER
- Liraglutide 3.0 mg
- Phentermine/topiramate ER

Weight Loss at 1 Year

- ≥ 5%
- ≥ 10%
Ability of Liraglutide 3 mg to Maintain and Promote Additional Weight Loss After Low-calorie Diet: SCALE Maintenance Study

Liraglutide Placebo:
- Liraglutide: n = 207
- Placebo: n = 206

Mean ± SD weight at run-in (week -12): 105.9 ± 22.1 kg

F = follow-up period; S = screening period.
Lorcaserin 10 mg bid: BLOOM Study Weight Change Over Two Years

There is a Variable Response to Weight Loss Therapy: It looks like this.

Medications for Chronic Weight Management: Contraindications and Related Precautions

- **Orlistat**
  - Chronic malabsorption syndrome (e.g., fat soluble vitamins/medications)
  - Cholestasis

- **Lorcaserin**
  - None other than pregnancy

- **Phentermine/topiramate ER**
  - Glaucoma
  - Hyperthyroidism
  - During/within 14 days of MAOI use
  - Topiramate: fetal oral clefts (regular pregnancy testing)

- **Naltrexone ER/bupropion ER**
  - Uncontrolled hypertension
  - Seizure disorders; anorexia nervosa or bulimia; abrupt discontinuation of some drugs
  - Use of other bupropion-containing products
  - Chronic opioid use (opioid withdrawal)
  - During/within 14 days of MAOI use

- **Liraglutide 3.0 mg**
  - MEN2, personal/family history of MTC (potential risk of thyroid C-cell tumors—rodent data)

All are contraindicated in pregnancy and generally not recommended for women who are breastfeeding; caution on use of reliable contraception.

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*a For all agents, known hypersensitivity to agent or any component.
*b Alcohol, benzodiazepines, barbiturates, antiepileptic drugs.
*c Relevance in humans has not been determined.

How Do We Use Available Treatment Modalities for Overweight and Obese Patients?

- Balance efficacy, safety, and cost
- Optimize benefit: risk ratio
- Achieve best outcomes
- Cost-effectiveness of care
# NHLBI Obesity Treatment Guidelines

## A Guide to Selecting Treatment

<table>
<thead>
<tr>
<th>BMI Category</th>
<th>Treatment</th>
<th>25–26.9</th>
<th>27–29.9</th>
<th>30–34.9</th>
<th>35–39.9</th>
<th>≥40</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diet, physical activity, and behavior</strong></td>
<td>Appropriate NHLBI Guidelines</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Pharmacotherapy</strong></td>
<td>No</td>
<td></td>
<td>With comorbidities</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Surgery</strong>*</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No LAGB only</td>
<td>With comorbidities</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*Bariatric surgeries require lifestyle medical follow-up.

*FDA approved gastric band surgery for patients with BMI ≥30 and one weight related medical condition (February 2011).

LAGB, laparoscopic adjustable gastric banding

AACE/ACE Clinical Practice Guidelines for Comprehensive Medical Care of Patients with Obesity


www.aace.com/publications/guidelines
The Mandate

An evidenced-based care model is needed that is:

(i) Comprehensive: all aspects of diagnosis, evaluation, treatment decisions, and treatment goals

(ii) Practical: applicable to real-world patient care

(iii) Evidence-Based: Considers the totality of the evidence pertinent to all key aspects of patient management

(iv) is designed to optimize benefit and risk based on defined outcomes that reflect impact of treatment on the health of the patient.
## What are we Treating?

**Q1.** Do the 3 phases of chronic disease prevention and treatment—ie, primary, secondary, and tertiary—apply to the disease of obesity?

**Q3.** What complications are attributable to obesity?

**Q4.** Does BMI or other measures of adiposity convey full information regarding the impact of excess body weight on the patient’s health?

## Why are we Treating it?

**Q5.** Do patients with excess adiposity and related complications benefit more from weight loss than patients without complications, and, if so, how much weight loss would be required?

## How do we Treat it?

**Q6.** Is lifestyle/behavioral therapy effective?

**Q7.** Is pharmacotherapy effective?

**Q8.** How to optimally individualize pharmacotherapy?

**Q9.** Is bariatric surgery effective?
Q1. Do the 3 phases of chronic disease prevention and treatment apply to the disease of obesity?
— i.e., primary, secondary, and tertiary
Chronic Disease Phases and Interventions

**PHASE**
- **Primary Prevention**
- **Secondary Prevention**
- **Tertiary Prevention**

**GOAL**
- Prevent disease from occurring
- Halt early progression and prevent sequelae (before complications)
- Reduce complications and prevent further deterioration (after complications)

**INTERVENTION**
- Eliminate risk factors
  - Primordial (population)
  - Primary (high risk)
- Prevent complications and worsening of the disease.
- Limit adverse consequences of a disease on health
Chronic Disease Model
(ie, obesity, diabetes, asthma, hypertension, lupus, etc.)

Genetics

DISEASE

Environment

Complications/
Disease Severity

Environment

Genetics
Obesity and 3 Phases of Chronic Disease Prevention and Treatment

• **Q1.** Do the 3 phases of chronic disease prevention and treatment—ie, primary, secondary, and tertiary—apply to the disease of obesity?

• **R2.** The modality and intensity of obesity interventions should be based on the primary, secondary, and tertiary phases of disease prevention; this 3-phase paradigm for chronic disease aligns with the pathophysiology and natural history of obesity and provides a rational framework for appropriate treatment at each phase of prevention

• (Grade C; BEL 4, upgraded due to high relevance to natural history of the disease).
AACE/ACE Algorithm for the Medical Care of Patients with Obesity


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**Patient Presentation**
- Screens positive for overweight or obesity
- BMI ≥25 kg/m² (≥23 kg/m² in some ethnicities)
- Presence of weight-related disease or complication that could be improved by weight loss therapy

**Evaluation**
- Medical history
- Physical examination
- Clinical laboratory
- Review of systems, emphasizing weight-related complications
- Obesity history: graph weight vs age, lifestyle patterns/preferences, previous interventions
- Confirm that elevated BMI represents excess adiposity
- Measure waist circumference to evaluate cardiometabolic disease risk

**Anthropometric Diagnosis**
- BMI kg/m²
  - < 25: NORMAL WEIGHT
  - 25 to 29.9: OVERWEIGHT
  - ≥ 30: OBESITY

**Clinical Diagnosis**
- Waist circumference below regional/ethnic cut-offs

**Checklist of Obesity-Related Complications**
(staging and risk stratification based on complication-specific criteria)
- None
- Mild to Moderate
- Severe

**Diagnostic Categories**
- NORMAL WEIGHT (no obesity)
- OVERWEIGHT BMI 25–29.9
- OBESITY BMI ≥30

**Phases of Chronic Disease Prevention and Treatment Goals**
- PRIMARY: Prevent overweight/obesity
- SECONDARY: Prevent progressive weight gain or achieve weight loss to prevent complications
- TERTIARY: Achieve weight loss sufficient to ameliorate the complications and prevent further deterioration

**Treatment Based on Clinical Judgment**
- Healthy meal plan
- Physical activity
- Health education
- Built environment
- Lifestyle/behavioral therapy
- Consider pharmacotherapy if lifestyle alone not effective
- Lifestyle/behavioral therapy
- Consider pharmacotherapy (BMI ≥27)
- Lifestyle/behavioral therapy
- Add pharmacotherapy (BMI ≥27)
- Consider bariatric surgery (BMI ≥35)

**Follow-Up**
- Once the plateau for weight loss has been achieved, re-evaluate the weight-related complications. If the complications have not been treated to target, then weight loss therapy should be intensified or complication-specific interventions need to be employed.
- Obesity is a chronic disease and the diagnostic categories for obesity may not be static. Therefore, patients require ongoing follow-up, re-evaluation, and long-term treatment.

Abbreviation: BMI = body mass index
Diagnosis: Anthropometric Component

EVIDENCE-BASED SCREENING AND DIAGNOSIS FOR EXCESS ADIPOSY IN CLINICAL SETTINGS

1. Clinical interpretation of BMI: Ensure elevated BMI is indicative of excess adiposity by assessing: age, gender, muscularity, hydration status, edema, third space fluid collection, large tumors, sarcopenia
2. Waist circumference if BMI <35 kg/m²: Adds information pertaining to cardiometabolic disease risk; use gender- and ethnicity-specific cut-off values
3. Can consider body composition technologies: eg, bioelectrical impedance, air/water displacement plethysmography, or dual-energy x-ray absorptiometry scan

Abbreviation: BMI = body mass index
# Diagnosis: Clinical Component

**Evaluate for a Checklist of Weight-Related Complications**

<table>
<thead>
<tr>
<th>Patients Present with Overweight or Obesity (Anthropometric Component)</th>
<th>Candidates for Weight Loss Therapy</th>
<th>Patients Present with Weight-Related Disease or Complication (Clinical Component)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients present with BMI $\geq 25$ kg/m$^2$, or $\geq 23$ kg/m$^2$ in certain ethnicities, and excess adiposity</td>
<td>Evaluate for weight-related complications</td>
<td>Prediabetes</td>
</tr>
<tr>
<td>Evaluate for overweight or obesity</td>
<td></td>
<td>Metabolic Syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Type 2 Diabetes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dyslipidemia</td>
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<tr>
<td></td>
<td></td>
<td>Hypertension</td>
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<tr>
<td></td>
<td></td>
<td>Cardiovascular Disease</td>
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<tr>
<td></td>
<td></td>
<td>Nonalcoholic Fatty Liver Disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Polycystic Ovary Syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Female Infertility</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Male Hypogonadism</td>
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<tr>
<td></td>
<td></td>
<td>Obstructive Sleep Apnea</td>
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<tr>
<td></td>
<td></td>
<td>Asthma/Reactive Airway Disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Osteoarthritis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Urinary Stress Incontinence</td>
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<tr>
<td></td>
<td></td>
<td>Gastroesophageal Reflux Disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Depression</td>
</tr>
<tr>
<td>Obesity Stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NORMAL WEIGHT</td>
<td>STAGE 0</td>
<td>STAGE 1</td>
</tr>
<tr>
<td>No obesity</td>
<td>No complications</td>
<td>One or more mild-to-moderate complications or may be treated effectively with moderate weight loss</td>
</tr>
<tr>
<td>BMI &lt;25 &lt;23 in certain ethnicities</td>
<td>BMI 25–29.9 overweight</td>
<td>BMI ≥30 obesity</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prevention Phase/ Treatment Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRIMARY</td>
</tr>
<tr>
<td>Prevent overweight / obesity</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Healthy meal plan</td>
</tr>
<tr>
<td>• Physical activity</td>
</tr>
<tr>
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<tr>
<td>• Add pharmacotherapy (BMI ≥27)</td>
</tr>
<tr>
<td>• Consider bariatric surgery (BMI ≥35)</td>
</tr>
</tbody>
</table>
3. Treatment Based on Clinical Judgment

**When to Initiate Weight-Loss Medications in Patients with Overweight/Obesity**

**Initiate Lifestyle Therapy**

1. **No Complications.**
   Patients with overweight or obesity who have no clinically significant weight-related complications (secondary prevention)

2. **Mild to Moderate Complications.**
   - Patients with mild to moderate weight-related complications when lifestyle therapy is anticipated to achieve sufficient weight loss to ameliorate the complication (tertiary prevention)
   - Note: weight loss medications may also be indicated based on clinical judgment

**Initiate Weight Loss Medication as an Adjunct to Lifestyle Therapy**

1. **Failure on Lifestyle Therapy.**
   Add medication for patients who have progressive weight gain or who have not achieved clinical improvement in weight-related complications on lifestyle therapy alone.

2. **Weight Regain on Lifestyle Therapy.**
   Add medication for patients with overweight (BMI 27–29.9 kg/m²) or obesity who are experiencing weight regain following initial success on lifestyle therapy alone.

3. **Presence of Weight-Related Complications.**
   Initiate medication concurrent with lifestyle therapy for patients with overweight (BMI 27–29.9 kg/m²) or obesity who have weight-related complications, particularly if severe, in order to achieve sufficient weight loss to ameliorate the complication (tertiary prevention).
<table>
<thead>
<tr>
<th>OBESITY COMPLICATION</th>
<th>% weight loss required for therapeutic benefit</th>
<th>Notes</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes Prevention</td>
<td>3% to 10%</td>
<td>Maximum benefit 10%</td>
<td>DPP (Lancet, 2009) SEQUEL (Garvey et al, 2013)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5% to &gt;15%</td>
<td>BP still decreasing &gt;15%</td>
<td>Look AHEAD (Wing, 2011)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>3% to &gt;15%</td>
<td>TG still decreasing at &gt;15%</td>
<td>Look AHEAD (Wing, 2011)</td>
</tr>
<tr>
<td>HbA1c</td>
<td>3% to &gt;15%</td>
<td>HbA1c still decreasing at &gt;15%</td>
<td>Look AHEAD (Wing, 2011)</td>
</tr>
<tr>
<td>NAFLD</td>
<td>10%</td>
<td>Improves steatosis, inflammation, mild fibrosis</td>
<td>Assy et al, 2007; Dixon et al, 2004; Anish et al, 2009</td>
</tr>
<tr>
<td>Sleep Apnea (AHI)</td>
<td>10%</td>
<td>Little benefit at ≤ 5%</td>
<td>Sleep AHEAD (Foster, 2009) Winslow et al, 2012</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>5-10%</td>
<td>Improves symptoms and joint stress mechanics</td>
<td>Christensen et al, 2007 Felson et al, 1992; Aaboe et al, 2011</td>
</tr>
<tr>
<td>Stress Incontinence</td>
<td>5-10%</td>
<td></td>
<td>Burgio et al, 2007 Leslee et al, 2009</td>
</tr>
<tr>
<td>GERD</td>
<td>5-10% women 10% men</td>
<td></td>
<td>Singh et al, 2013 Tutujian R, 2011</td>
</tr>
</tbody>
</table>
Phentermine/Topiramate ER and the Prevention of Diabetes in Patients With Metabolic Syndrome and/or Prediabetes: SEQUEL Study

Dose-Response for Weight Loss and Diabetes Prevention due to Phentermine/Topiramate ER Treatment: SEQUEL

Garvey et al, Diabetes Care, 37:912, 2014
How Much Weight Loss Is Needed to Prevent T2DM?

DPP Experience

Incidences of Diabetes After Bariatric Surgery

UK Population-Based Matched Cohort Study*

*Matched for BMI, age, gender, index year, and A1C.

BMI = body mass index.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Criteria</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No Risk Factors</td>
<td>Healthy Obese ¹</td>
</tr>
<tr>
<td>1</td>
<td>1 or 2 Risk Factors (waist, blood pressure, triglycerides, HDL-c)</td>
<td>Metabolic Syndrome has low sensitivity for CMD, and 1 or 2 risk factors elevates risk of future T2DM and CVD ²,³</td>
</tr>
<tr>
<td>2</td>
<td>Metabolic Syndrome OR Prediabetes</td>
<td>Both Metabolic Syndrome and Prediabetes confer increased risk of T2DM and CVD ³,⁴</td>
</tr>
<tr>
<td>3</td>
<td>Metabolic Syndrome PLUS Prediabetes</td>
<td>Risk of future T2DM is double in patients with both Metabolic Syndrome and Prediabetes compared with either alone ³-⁶</td>
</tr>
<tr>
<td>4</td>
<td>End-Stage Cardiometabolic Disease Type 2 Diabetes and/or CVD</td>
<td>T2DM is CVD risk equivalent ⁷</td>
</tr>
</tbody>
</table>

Cardiometabolic Disease Staging: Cumulative Diabetes Incidence as a Function of Increasing CMDS Risk Stage: CARDIA Study Cohort

Cumulative incidence of T2D in the phase III studies of phentermine/topiramate ER as a function of weighted cardiometabolic disease staging

CMDS score / treatment arm

- 0–29/Treatment
- 60+/Treatment
- 0–29/Placebo
- 60+/Placebo

Diabetes rate (%)

CMDS 60+
Placebo vs. drug

CMDS 0–29
Placebo vs. drug


CMDS, Cardiometabolic Disease Staging; ER, extended release; T2D, type 2 diabetes
Number needed to treat to prevent one case of T2D as a function of baseline weighted cardiometabolic disease staging

<table>
<thead>
<tr>
<th>CMDS score</th>
<th>Number needed to treat</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–29</td>
<td>258</td>
</tr>
<tr>
<td>60+</td>
<td>18</td>
</tr>
</tbody>
</table>

CMDS, Cardiometabolic Disease Staging; T2D, type 2 diabetes

PREDIABETES ALGORITHM

IFG (100–125) | IGT (140–199) | METABOLIC SYNDROME (NCEP 2005)

LIFESTYLE MODIFICATION
(Including Medically Assisted Weight Loss)

OTHER CVD RISK FACTORS

WEIGHT LOSS THERAPIES

ANTIHYPERTHYBLIC THERAPIES
FPG > 100 | 2-hour PG > 140

CVD RISK FACTOR MODIFICATIONS ALGORITHM
DYSLIPIDEMIA ROUTE
HYPERTENSION ROUTE

NORMAL GLYCEMIA
Progression

OVERT DIABETES

PROCEED TO HYPERGLYCEMIA ALGORITHM

1 PRE-DM CRITERION
Intensify Weight Loss Therapies
Low-risk Medications
Metformin
Acarbose

MULTIPLE PRE-DM CRITERIA
Consider with Caution
TZD
GLP-1 RA

If glycemia not normalized, consider with caution

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In Summary

• AACE Obesity Guidelines constitute an evidenced based model for patient care that encompasses screening, diagnosis, staging, treatment decisions, goals of therapy, and follow-up.

• Establishes a diagnostic approach that incorporates both an assessment of adiposity and the impact of excess adiposity on health as manifest by weight-related complications.

• Guides treatment modality and intensity based on the phases of chronic disease prevention and treatment, and the risk, presence, and severity of weight-related complications.

• Establishes desired outcomes and goals of therapy that do not simply reflect the amount of weight lost but the improvements in patient health.

• Emphasizes a patient-centric approach for individualization of therapy to optimize effectiveness, patient safety, and the benefit/risk ratio.

• A model that can be rationally adopted by health care systems with integration into overall portfolios of patient care.
THANK YOU!