The Metabolic Syndrome
Why Obesity is Bad News

Jerry M. Blaine, MD
History

- 1923 Highland: described clustering of hypertension, hyperglycemia, and gout
- 1979 Vague: described association between T 2 DM, C-V disease and male pattern obesity
- 1988 Reaven: Syndrome X; insulin resistance a common denominator
- 1998 WHO: Metabolic Syndrome
Definition

Cluster of Risk factors:
- atherogenic dyslipidemia
- glucose intolerance
- elevated blood pressure
- a pro-inflammatory state
- a pro-thrombotic state

A result of abdominal obesity and insulin resistance

Under-recognized, under-diagnosed and under-treated
NCEP Criteria

Three of the following five:

- elevated waist circumference
- elevated triglycerides
- low HDL
- BP over 130/85
- fasting glucose >100 (>5.6 nmol/L)

(A1C not yet included, although now a component of diagnosis of diabetes)
A Shifting Profile for Cardiometabolic Risk

- High low-density lipoprotein cholesterol (LDL-c) levels and hypertension have been and continue to be the primary targets of risk management.
- Future treatments need to more effectively address atherogenic dyslipidemia and emerging risk factors associated with abdominal adiposity.
Obesity* Trends Among US Adults:
BRFSS† — 1990, 1995, 2005

(*BMI ≥30, or about 30 lbs overweight for a 5’4” person)

†CDC web site, from: Behavioral Risk Factor Surveillance System (BRFSS).
Obesity and Diabetes Trends Among US Adults: BRFSS — 1990-2001

Metabolic syndrome prevalence in a multicultural population in Auckland, New Zealand

- Table 1. Metabolic syndrome prevalences (%) by ethnic group (Maori, Pacific, and Others) in adults aged 35–74 years from the Diabetes, Heart and Health Study 2002-03

<table>
<thead>
<tr>
<th>Ethnic Group</th>
<th>Metabolic Syndrome Prevalence (%)</th>
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<tr>
<td></td>
<td>Men</td>
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<tr>
<td>Others</td>
<td>17% (N: 2021)</td>
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<td>Maori</td>
<td>34% (N: 1006)</td>
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<td>Pacific</td>
<td>41% (N: 996)</td>
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<td>Women</td>
<td>15%</td>
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<td>All</td>
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NZMJ 26 January 2007, Vol 120 No 1248
Twin Epidemics: Parallels in Prevalence

~61% of US Adults Are Overweight or Obese

Overweight/Obesity

Metabolic Syndrome

Prevalence, %

Age, yr

Note: Overweight is defined as BMI \( \geq \) gender- and weight-specific 95th percentile from the 2000 CDC Growth Charts.

Source: National Health Examination Surveys II (ages 6-11) and III (ages 12-17); National Health and Nutrition Examination Surveys I, II, III and 1999-2004, NCHS, CDC.

Atherosclerosis In Youth Is Linked To Obesity and “Early” Insulin Resistance

**Fatty Streaks**
Men: Age 15-24

<table>
<thead>
<tr>
<th>BMI (kg/m²)</th>
<th>Aortic Strips</th>
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<td>&lt; 25</td>
<td><img src="image1" alt="Image" /></td>
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<tr>
<td>&gt; 30</td>
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**Raised Lesions**
Men: Age 15-24

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<td>&gt; 30</td>
<td><img src="image6" alt="Image" /></td>
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Relationship Between Body Mass Index (BMI) and Cardiovascular Disease Mortality

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<th>Body Mass Index</th>
<th>Relative Risk of Death</th>
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<td>20.5–21.9</td>
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<td>&gt;39.9</td>
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How Effective Are Current Treatments?
Residual Cardiovascular (CV) Risk in Statin-Treated Patients

The MRC/BHF Heart Protection Study

Residual Cardiovascular (CV) Risk in Statin-Treated Patients

Risk Reduction = 24% (*P* < 0.0001)

Event Rate = 19.8%*

*19.8% of statin-treated patients had a major CV event by five years.

TNT: Substantial Risk Persists Despite Maximal Dose Atorvastatin in Prediabetes and Diabetes

Deedwania P, for TNT. Lancet. 2006;368: 919-928.

**All Metabolic Syndrome**
- Atorvastatin 10 mg (N=2820)
- Atorvastatin 80 mg (N=2764)

\[ P<0.0001 \]

**Metabolic Syndrome, No Diabetes**
- Atorvastatin 10 mg (N=2191)
- Atorvastatin 80 mg (N=2162)

\[ P=0.0002 \]

CHD, coronary heart disease.

Deedwania P, for TNT. Lancet. 2006;368: 919-928.
## Impact of Gluco-Metabolic Characteristics on Risk of Major Cardiovascular Events in TNT

### All Patients

<table>
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<th>Characteristic</th>
<th>HR</th>
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<td>Low HDL-C</td>
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<td>Fasting Glucose ≥100 mg/dL</td>
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<tr>
<td>Body Mass Index ≥28 kg/m²</td>
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<tr>
<td>Triglycerides ≥150 mg/dL</td>
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<td>Hypertension</td>
<td>1.48</td>
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*P<0.0001; †P=0.0009; ‡P=0.015.

The Steno-2 Study

Multiple CV Risk Factor Management in Diabetes: The Best, and Not Enough

*Death from CV causes, nonfatal myocardial infarction, coronary artery bypass graft, percutaneous coronary interventions, nonfatal stroke, amputation resulting from ischemia, or surgery for peripheral atherosclerotic artery disease.

†Behavior modification and pharmacologic therapy.

‡Primary composite end-point: conventional therapy (44%) vs intensive therapy (24%).

What About Residual Cardiometabolic Risk After Treatment of Established CV Risk Factors?

- Triglycerides
- High-density lipoprotein (HDL) cholesterol
- Inflammation
- Glucose
Current Therapies Often Address Individual Risk Factors

- Waist circumference
- Blood pressure
- Blood glucose
- Triglycerides
- HDL-cholesterol
- LDL-cholesterol
- Insulin resistance
- Thrombotic risk

NCEP ATP III definition of the metabolic syndrome

- Antihypertensives
- Oral antidiabetic agents
- Lipid modifiers
- Insulin sensitizers
- Antiplatelet agents
How Obesity Causes Disease:
The Fat Cell—A Multi-endocrine Organ

DM=diabetes mellitus; FFA=free fatty acid; PAI-1=plasminogen activator inhibitor-1; TNFα=tumor necrosis factor-alpha; IL-6=interleukin 6; ASCVD=atherosclerotic cardiovascular disease.

Bray, G. J Clin Endocrinol Metab. 2004;89:2583-2589.
Slide: After Dr. G. Bray.
Metabolic Syndrome and Acute MI in the Young (<45 yrs.)

AT LAHEY CLINIC

161 consecutive patients <45 years of age with acute MI transferred for emergency PCI

• 76 or 47% met NCEP criteria for Metabolic Syndrome

  -- 6 had previous diagnosis of Type 2 diabetes

  -- 10 had new diagnoses of T2DM at MI or within 3 months

Am J Cardiol  2007
The Drivers of Cardiometabolic Risk
Unmet Clinical Needs to Address in the Next Decade

Classic Risk Factors
- LDL-C
- BP
- Smoking

Major Unmet Clinical Need
- Metabolic Syndrome
  - Abdominal Adiposity
  - Insulin
  - Glu
  - PAI-1
  - TG
  - HDL-C

Novel Risk Factors
- TNFα
- IL-6
- T2DM

CARDIOVASCULAR DISEASE
Obesity and Abdominal Adiposity Are Leading Drivers of Cardiometabolic Risk

Body size

- BMI
- Abdominal adiposity

Insulin resistance

Glucose metabolism
- PP-glucose
- IFG
- IGT
- T2DM

Uric acid metabolism
- Uric acid
- Urinary uric acid clearance

Dyslipidemia
- TG
- PP lipemia
- HDL-C
- Small, dense LDL

Hemodynamic
- SNS activity
- Na retention
- Hypertension

Inflammation/Thrombosis
- CRP
- PAI-1
- Fibrinogen

CORONARY HEART DISEASE

Growing Prevalence of Abdominal Adiposity

US National Health and Nutrition Examination Survey (NHANES)

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<tbody>
<tr>
<td>Men</td>
<td>29.5%</td>
<td>42.4%</td>
<td>+44%</td>
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<tr>
<td>Women</td>
<td>47.0%</td>
<td>61.3%</td>
<td>+30%</td>
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</table>

Abdominal adiposity defined as waist circumference: >102 cm (>40 in) in men or >88 cm (>35 in) in women

Data are adjusted for age.
Abdominal Adiposity and Associated CVD Risk Factors

Patients with abdominal adiposity (high waist circumference) often present with one or more additional CVD risk factors.
Visceral Fat: The Critical Adipose Depot

- Place a measuring tape in a horizontal plane at the level of the iliac crest, without compressing the skin.
- The value is read at the end of a normal expiration.
Why Is Abdominal Adiposity Harmful?

- Abdominal adiposity
  - is often associated with other CVD risk factors
  - is an independent CVD risk factor
- Adipocytes are metabolically active endocrine organs, not simply inert fat storage

The Evolving View of Adipose Tissue: An Endocrine Organ

Old View: Inert Storage Depot

Fed
- Fatty acids
- Glucose

Fasted
- Fatty acids
- Glycerol

Current View: Secretory/Endocrine Organ

Multiple secretory products

Insulin Resistance is associated with or directly responsible for factors causing atherothrombosis.

- Adiponectin ↓
- MMP-9 ↑
- CRP ↑
- CD 40 ↑
- Platelet Aggregation ↑
- Fibrinogen ↑
- vWF ↑
- F VII ↑
- F VIII ↑
- Tissue Factor ↑

Coronary Artery

- Plaque Formation ↑
- Endothelial Cell Dysfxn ↑
- CV RFs Hyperglycemia oxidative stress ↑

Thrombus

- Plaque Disruption

Sympathetic Tone ↑

- PAI-1 ↑
- TPA ↓
- PG12 ↓
- Endothelin ↑

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Insulin Resistance – A Major Driver of Atherosclerosis and Cardiovascular Disease

- Dyslipidemia
- Elevated Blood Pressure
- Macrophage Infiltration
- Hyperglycemia
- Inflammatory Cytokines
- Endothelial Function
- Hyperinsulinemia
- Smooth Muscle Proliferation

Image: Fibrolipid AS plaque with Hemorrhage (low mag)
Potential Role of Mitochondria Development of Diabetes, Obesity and the Metabolic Syndrome

Mitochondria – The Powerhouse of the Cell

- Mitochondria are involved in converting all nutritional fuels into energy
- Mitochondrial activity is decreased in aging, obesity and type 2 diabetes.
- Mitochondrial activity is increased with exercise training and dietary manipulations that improve metabolism.
Impact of Weight Loss on Adipose Tissue Hormone Production

**Increases**
- Adiponectin

**Decreases**
- C-reactive protein
- IL-6
- TNFα
- Leptin
- FFA

**Result:**
- Improved insulin sensitivity, reduced inflammation
- Reduces risk of type 2 diabetes, ASCVD, other comorbidities
# Impact of Weight Loss on Risk Factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>~5% Weight Loss</th>
<th>5%–10% Weight Loss</th>
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<td>HbA₁c</td>
<td><img src="image1" alt="1" /></td>
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<tr>
<td>Blood Pressure</td>
<td><img src="image2" alt="2" /></td>
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<tr>
<td>Total Cholesterol</td>
<td><img src="image3" alt="3" /></td>
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<tr>
<td>HDL Cholesterol</td>
<td><img src="image3" alt="3" /></td>
<td><img src="image3" alt="3" /></td>
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<tr>
<td>Triglycerides</td>
<td><img src="image4" alt="4" /></td>
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</table>

Patient Evaluation and Classification
Traditional Treatment Approach

Dyslipidemia
- Lipid panels
- Statins
- Fibrates
- Niacin
- Resins

Hypertension
- BP
- Ambulatory BP
- Sodium
- K++
- ACEI
- ARB
- Diuretic
- Ca-channel blockers

Type 2 Diabetes
- Blood sugar
- Glycosylated hemoglobin
- Sugar
- Distribute CHO, Pro, Fat
- Metformin
- Insulin
- TZDs
- Sulfonylureas
- Alpha-glucosidase inhibitors

Weight


Adapted from Dr. Caroline M. Apovian.
New Treatment Approach

Adipose Tissue

- Reduce BMI and waist circumference
  - Calories, glycemia
  - Daily activity/exercise
  - Behavior therapy
  - d/c medications causing weight gain
  - Current medications, medications in development, combination therapy

Dyslipidemia

- Diet
  - ↑ Omega-3s
  - ↑ MUFA
  - ↓ Sat and trans fat
  - ↓ Glycemia + ETOH
    - ATP III guidelines: TLC diet
- Meds
  - Statins
  - Fibrate
  - Ezetimibe

Hypertension

- Diet
  - DASH
  - ↓ Na
  - ↓ ETOH
- Meds
  - ACEI
  - ARB
  - Aliskiren

Hyperglycemia

- Fiber
- Glycemic diet

Meds
- Metformin
- Exenatide
- Pramlintide
- DPP-IV inhibitors

Adapted from Dr. Caroline M. Apovian.
Weight is Controlled by a Feedback System

Weight loss provokes counter-regulatory responses

Afferent

Stimulate Intake

NPY
AGRP
galanin
Ghrelin
GLP-1
CCK
Vagus
Endocannabinoids

Inhibit

α-MSH
Dynorphin
CRH/UCN
Endocannabin.
GLP-I
CART
NE
5-HT

External Factors
food availability, palatability

Gut and Liver

Meal Size

Energy Balance and Adipose Stores

Food Intake

Energy Expenditure

Efferent

Adiponectin


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Assessment and Management

- Measure height and weight, estimate BMI
- Measure waist circumference
- Review the patient’s medical condition
  - Assess comorbidities
    - How many are present and how severe are they?
    - Do they need to be treated in addition to the effort at weight loss?
# Use a BMI Table

## Body Mass Index (BMI) TABLE

<table>
<thead>
<tr>
<th>Weight (pounds)</th>
<th>120</th>
<th>130</th>
<th>140</th>
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### BMI Formula

- **BMI = weight (pounds) / height squared (inches²)**
- **Waist Circumference** - Increased risk: >35" for women, >40" for men


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### Assessing Obesity: BMI, Waist Circumference, and Disease Risk

<table>
<thead>
<tr>
<th>Category</th>
<th>BMI</th>
<th>Disease Risk Relative to Normal Weight and Waist Circumference</th>
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<tr>
<td></td>
<td>Men ≤40 in†</td>
<td>Men &gt;40 in</td>
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<tr>
<td></td>
<td>Women ≤35 in†</td>
<td>Women &gt;35 in</td>
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<tr>
<td>Underweight</td>
<td>&lt;18.5</td>
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<td>Normal*</td>
<td>18.5–24.9</td>
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<tr>
<td>Overweight</td>
<td>25.0–29.9</td>
<td>Increased High</td>
</tr>
<tr>
<td>Obesity</td>
<td>30.0–34.9</td>
<td>High Very high</td>
</tr>
<tr>
<td></td>
<td>35.0–39.9</td>
<td>Very high Very high</td>
</tr>
<tr>
<td>Extreme obesity</td>
<td>≥40</td>
<td>Extremely high Extremely high</td>
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</table>

*An increased waist circumference can denote increased disease risk even in persons of normal weight.¹

†For people of **Chinese, Japanese, or South Asian descent, and for ethnic South and Central Americans**, the cutpoints are 35.4 inches and 31.5 inches for males and females, respectively.²

---

Review Patient Medical History

Many aspects of the history are helpful in managing the obese patient

- Affect outcome
  - Family history
  - Age of onset of obesity
  - Minimum and maximum weight as an adult
  - Events associated with weight gain
  - Recent weight-loss attempts
  - Previous weight-loss modalities used successfully and unsuccessfully, and their complications
  - Cigarette smoking can complicate treatment
    - When stopping, weight is often gained
History

- Contraindications to treatment
  - Active cancer
  - Any severe, acute illness
  - Pregnancy

- Relative contraindications to treatment or need for specialized treatment
  - History of eating disorders, such as binge eating and purging by vomiting or laxative abuse
  - Alcohol and substance abuse

- Guides to treatment
  - Current level of physical activity
  - Understanding of nutrition
Exam

- **Blood pressure**
  - Use the correct size cuff

- **Acanthosis nigricans, skin tags**
  - Skin lesions that are darker than the skin around them; velvety feel; form in the folds along the neck, armpits, groin, knuckles and between the legs, at the elbow, under the breasts, and around the umbilicus

- **Thyroid**
  - Treatment will not help weight loss

- **PCOS**
  - Hirsutism
Recommended Labs*

- Comprehensive metabolic panel, including
  - Liver function tests
    - Abnormalities may suggest nonalcoholic fatty liver disease
  - Serum creatinine
  - Blood urea nitrogen
- Lipids
  - Triglycerides, high-density lipoprotein, low-density lipoprotein, total cholesterol
- Glucose
  - Fasting glucose
  - HbA\textsubscript{1C}, two-hour PPG (in patients with diabetes)
- Thyroid-stimulating hormone
- Urinalysis
  - Should also do spot microalbumin\textsuperscript{†} if patient has other comorbidities

*Labs should be in a fasting state, unless otherwise noted.
\textsuperscript{†} With albumin-specific dipstick.
Other Labs to Consider

- **Glucose**
  - Oral glucose tolerance test (in patients without diabetes)

- **High sensitivity or “cardio” C-reactive protein**
  - Often elevated
  - Good for demonstrating health benefits of weight loss

- **Insulin**
  - Fasting and two-hour postprandial

- **Uric acid**
Use a “Weight-Centered” Approach to Manage the Obese Patient

- Look for:
  - Obstructive sleep apnea (OSA)
  - Medications causing weight gain
    - Substitute alternatives that are weight-neutral or associated with weight loss
      - Example: sulfonylurea to metformin
  - Depression
    - Treat or refer to specialist
  - Pre-diabetes, hyperinsulinism, IFG, PCOS
    - Use low glycemic, high fiber, low energy density diet
    - Use metformin, acarbose

Obstructive Sleep Apnea

- Often overlooked in obese patients
- History of loud snoring
  - Cessation of breathing during sleep, which is often followed by a loud clearing breath and then brief awakening
  - Restless sleeper; some persons find that they can only sleep comfortably in the sitting position
  - Partner may best describe these symptoms
  - Daytime fatigue with episodes of sleepiness at inappropriate times
Obstructive Sleep Apnea (cont.)

- CVD is common in patients with OSA
- Increased risk for
  - Cardiac arrhythmias, including severe bradycardias, during apneic episodes
  - Angina and myocardial infarction
  - Dilated cardiomyopathy (reversible with successful treatment)
  - Cerebrovascular events
- In some patients, repetitive severe nocturnal oxyhemoglobin desaturations may lead to persistent pulmonary hypertension and cor pulmonale
  - More common in patients with comorbid COPD
- Psychosocial problems are also common (e.g., mood changes, poor memory, irritability, impaired concentration)

Obstructive Sleep Apnea (cont.)

- **Exam**
  - Hypertension
  - Pulmonary hypertension (loud P2)
  - Narrowing of the upper airway
  - Scleral injection
  - Leg edema secondary to pulmonary hypertension

- **Laboratory studies**
  - May show polycythemia

- **Referral to a pulmonologist or sleep specialist is appropriate**

- **May lead to further weight gain if not treated**
Talking to Your Patient

Treat cardiometabolic risk the way you treat other chronic conditions

- Assess weight in an empathetic, nonjudgmental fashion
- Avoid criticizing patients; help them identify and solve problems preventing success
- Discuss success in terms of nonweight outcomes
  - Lipids
  - Glucose
  - HTN
  - Mobility
  - Sleep quality/energy level

Treatment of “Metabolic Syndrome” or “Cardiometabolic Risk”
According to guidelines from
- Adult Treatment Panel III (ATP III)*
- The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VII)†
- American Diabetes Association (ADA)‡

First-Line Therapy = Weight Reduction With Lifestyle Modification

A Guide to Selecting Treatment: National Institutes of Health (NIH) Guidelines*

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<th>Treatment</th>
<th>25–26.9</th>
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<th>35–39.9</th>
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<td>Yes, with comorbidities</td>
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<td>Weight-loss surgery</td>
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<td>Yes, with comorbidities</td>
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</table>

*Yes alone indicates that the treatment is indicated regardless of the presence or absence of comorbidities. The solid arrow signifies the point at which therapy is initiated.

Complications: Medications That Cause Weight Gain/Prevent Weight-Loss

- Drugs used to treat the following problems have been shown to cause weight gain and prevent obesity treatment from being effective:
  - Depression
  - Seizures
  - Insomnia
  - Schizophrenia
  - Hypertension
  - Allergies
  - Mood disorders
  - Diabetes
  - Birth control

- Weight gain is a cause of abnormal lipid profile

You may need to consider a substitute

Drugs That May Promote Weight Gain

- Diabetes treatments
  - Insulin
  - Sulfonylureas
  - Thiazolidinediones

- Psychiatric/neurologic
  - Antipsychotics
  - Antidepressants
  - Antiepileptics
  - Lithium

Drugs That May Not Promote Weight Gain

- Diabetes treatments
  - Exenatide, pramlintide, sitagliptin
  - Metformin
  - Acarbose, miglitol

- Psychiatric/neurologic
  - Ziprasidone, aripiprazole
  - Bupropion
  - Topiramate, zonisamide, lamotrigine

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<table>
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<th>Drugs or Alternatives That May Promote Weight Gain</th>
<th>Drugs or Alternatives That May Not Promote Weight Gain</th>
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<td>- NSAIDs</td>
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<td>• Hormonal contraceptives</td>
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<td>• Progestational steroids</td>
<td>- Weight loss for menometrorrhagia</td>
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<td>• Antihistamines</td>
<td>• Steroid inhalers</td>
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<td>• $\alpha$-adrenergic blockers$^3$, $\beta$-adrenergic blockers (eg, metoprolol$^4$)</td>
<td>• ACE inhibitors, Ca blockers, diuretics, carvedilol$^4$</td>
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<tr>
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Portions taken from 2007 Cardiometabolic Support Network
Losing Weight –
The Importance of Physical Activity

- Physical activity generally **does not**
  - Result in substantial weight loss
  - Increase short-term diet-induced weight loss
- Physical activity **does**
  - Decrease loss of fat-free mass associated with weight loss
  - Improve CV health independent of weight loss
  - Support maintenance of weight loss
- There is also some evidence that physical activity may preferentially reduce intraabdominal fat

Lifestyle Modification in the Diabetes Prevention Program

- Months 1–6: 16 individual sessions with a registered dietitian (RD)
- Months 7–36: Minimum of 1 session every other month with RD
  - Additional support as needed
- Focus of sessions
  - Review food and activity records
  - Problem-solve difficulties
  - Praise participant's effort

Modest Weight-Loss Reduces the Incidence of New-Onset Diabetes in an At-Risk Population

Cumulative Incidence of Diabetes (%)

Placebo
Metformin
Lifestyle

P<0.001 for each comparison.

*Decrease in risk of developing diabetes, compared to placebo group.

Use a Variety of Tools, Keep it Simple, Keep it Going, Keep it Measurable

- Pedometer
- Food and activity records
- Meal replacements
- Reduce a category of food
- Cut all portions in half
“What fits your busy schedule better, exercising one hour a day or being dead 24 hours a day?”