Getting to the Heart of the Matter: Metabolic Syndrome

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Program Goals

• Explain metabolic syndrome
• Outline the cardiovascular consequences of the syndrome
• Discuss the management of metabolic syndrome.
• Identify the pharmacist’s role in identifying and managing patients with metabolic syndrome.
Metabolic Syndrome

• Synonyms
  • Insulin resistance syndrome
  • Syndrome X
  • Dysmetabolic syndrome
  • Multiple metabolic syndrome
  • Cardiometabolic syndrome
Metabolic Syndrome

If any 3 of the 5 are present

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Defining Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal obesity (waist circumference)</td>
<td>&gt; 40 in. (men)</td>
</tr>
<tr>
<td></td>
<td>&gt; 35 in. (women)</td>
</tr>
<tr>
<td>Elevated triglycerides*</td>
<td>≥ 150 mg/dl</td>
</tr>
<tr>
<td>Low HDL cholesterol*</td>
<td>&lt; 40 mg/dl (men)</td>
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<td></td>
<td>&lt; 50 mg/dl (women)</td>
</tr>
<tr>
<td>Hypertension*</td>
<td>≥ 130/ ≥ 85 mm Hg</td>
</tr>
<tr>
<td>Impaired fasting glucose*</td>
<td>≥ 100 mg/dL</td>
</tr>
</tbody>
</table>

* Or drug treatment for the condition

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Metabolic Syndrome

• Causes
  • Acquired causes
    • Overweight and obesity
    • Physical inactivity
  • Genetic causes

Obesity is on track to overcome smoking as leading cause of death
Healthy Lifestyle Characteristics Among Adults in the United States, 2000

• 3% of population leads a healthy lifestyle
  • nonsmoking
  • healthy weight (BMI 18.5 – 25)
  • 5 or more fruits & vegetables/day
  • regular physical activity (≥ 30 minutes for ≥ 5 times/week)

*Arch Intern Med* 2005;165:854-857
Metabolic Syndrome

- Prevalence
  - ~24% of US men and women
    - 4.6% of normal weight men, 22.4% of overweight, and 59.6% of obese
    - Caucasian – men 24.3%, women 22.9%
    - African American – men 13.9%, women 20.9%
    - Mexican American – men 20.8%, women 27.2%
  - ~ 44% of over 50 population
  - Estimated at 47 million Americans
Metabolic Syndrome

• Prevalence
  • 4.2% of adolescents (12-19)
    • 50% of severely obese
    • 28.7% of overweight
    • 6.1% of borderline high weight
    • 0.1% of normal weight
  • Criteria in adolescents
    • 3 or more: TG $\geq$ 110 mg/dL, HDL-C $\leq$ 40 mg/dL
    • FBG $\geq$ 110 mg/dL, BP at or above the 90th percentile for age, sex and height, waist circumference at or above the 90th percentile for age and sex
Age-Specific Prevalence of Metabolic Syndrome in US Adolescents and Adults, 1988-1994

Prevalence (%)

Age (yr)

Male
Female

WEAPONS OF MASS EXPANSION.
Why is Metabolic Syndrome a Bad Thing?
Atherogenic Consequences of Metabolic Syndrome

EXCESS WEIGHT → Hyperinsulinemia

→ Insulin Resistance

→ Glucose Intolerance

↓ HDL

↑ TG

→ Small dense LDL

→ Prothrombotic & Proinflammatory state

→ Macrovascular Disease
Anatomy of Fat Deposits

- Visceral fat = intraperitoneal and extraperitoneal fat
  - Most responsible for health hazards
  - Excess is an independent risk factor for type 2 DM, dyslipidemia, hypertension, and cardiovascular disease
  - Increased FFAs
- Subcutaneous fat
  - SQ fat
Chain of Events Leading to Cardiovascular Mortality

Coronary Thrombosis

Myocardial Infarction

Loss of Muscle

Neurohormonal Activation

Remodeling

Ventricular Dilation

Heart Failure

Death

Arrhythmia

Myocardial Infarction

Remodeling

Ventricular Dilation

Heart Failure

Death

CAD

Atherosclerosis

Myocardial Ischemia

Atherosclerosis

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Risk of MI, Stroke, Diabetes, or Death with Metabolic Syndrome

- 2-fold ↑’d risk of MI or stroke compared with those without the disease
- 5-fold ↑’d risk for developing type 2 diabetes
- Relative risk of CHD mortality = 3.77%

J Am Coll Cardiol 2004;43:475A
JAMA 2002;288:2709-16
ACC 52nd Annual Scientific Session: Abstract 845-6. March 2003
Atherosclerosis Timeline

From first decade: Growth mainly by lipid accumulation
From third decade: Smooth muscle and collagen
From fourth decade: Thrombosis, hematoma

Atherosclerosis and Inflammation
C Reactive Protein (CRP)

- Marker of inflammation which may be used as a predictor of degree of atherosclerosis in the body and as a predictor for developing CVD, stroke, and peripheral arterial disease.
- CRP is produced by the liver in response to “cues” from the blood vessel wall, macrophages, the heart and adipose tissue.
- In some studies, CRP is a stronger predictor of CV events than LDL.
- There are problems with using CRP:
  - Specificity
Stroke and CRP

- Honolulu Heart Program - Men with few cardiovascular risk factors but highest CRP levels had 3.8 fold increased incidence of stroke in 10 to 15 years compared to men with lowest CRP levels

- Women’s Health Study and Framingham Study – Associations between CRP levels and stroke risk
CDC and American Heart Association Recommendations on Measuring hs-CRP

• Optional to measure as an adjunct to other risk factors to further assess absolute risk for primary prevention in persons with intermediate/moderate risk (10 year CHD risk of 10-20%)

• Relative risk categories
  • <1.0 mg/L – low risk
  • 1-3 mg/L – average risk
  • > 3 mg/L - high risk

Circulation 2003;107:499-511
Diabetes is a Cardiovascular Disease

- 2/3 die of heart or blood vessel disease
- Risk of MI = risk of patient w/o diabetes who already has had MI
- Cardiovascular risk equivalent under ATP III
- Macrovascular complications begin before diagnosis
  - Ticking Clock Hypothesis
  - Metabolic syndrome patient
The clock begins ticking for atherosclerosis years before diagnosis of diabetes.
Metabolic Syndrome - Goals

• Prevention of type 2 diabetes
• Reduce risk of clinical atherosclerotic disease
Metabolic Syndrome - Therapeutic Objectives

- To reduce underlying causes
  - Lifestyle Modification
    - Dietary changes
    - Weight loss or control
    - Physical activity
- To treat associated lipid and non-lipid risk factors
  - Hypertension
  - Prothrombotic state
  - Atherogenic dyslipidemia
  - Diabetes or impaired glucose tolerance
  - Smoking cessation
Metabolic Syndrome - Treatment

• Reduce simple carbohydrates
• Increase complex carbohydrates
• Reduce saturated fats, trans fats, and cholesterol
• Increase fish
Metabolic Syndrome - Treatment

- **Weight loss**
  - Enhances LDL lowering
  - Reduces metabolic syndrome risk factors
  - Initial goal
    - 7-10% of body weight in first year
  - Continue weight loss thereafter to extent possible
  - Ultimate goal
    - BMI < 25 kg/m²
BMI - Determination

BMI = Wt (kg) ÷ Ht (m)² or

\[
BMI = \frac{Wt \ (lb) \times 703}{Ht \ (in)^2}
\]

Example: Wt 220, Ht 68” = \(\frac{220 \times 703}{68^2}\) = \(\frac{154,660}{4624}\)

BMI = 33.5
### Do You Know Your Own BMI?

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## Weight Guidelines

<table>
<thead>
<tr>
<th>Weight category</th>
<th>Obesity class</th>
<th>BMI</th>
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<tbody>
<tr>
<td>Underweight</td>
<td></td>
<td>&lt;18.5</td>
</tr>
<tr>
<td>Normal</td>
<td></td>
<td>18.5–24.9</td>
</tr>
<tr>
<td>Overweight</td>
<td>I</td>
<td>25.0–29.9</td>
</tr>
<tr>
<td>Obesity</td>
<td>II</td>
<td>30.0–34.9</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>35.0–39.9</td>
</tr>
<tr>
<td>Extreme obesity</td>
<td></td>
<td>≥40</td>
</tr>
</tbody>
</table>

Percentage of Population Obese by Self-Reported Weight/Height

- 60.5% overweight
- 23.9% obese

overweight/obese ≠ metabolic syndrome
BMI - Advantages

• More accurate measure of total body fat compared with body weight alone
• Consistent with other, more precise measures of body fatness
• Predictor of disease
• Easy and inexpensive to obtain
BMI - Limitations

• Very muscular people
• People who have lost muscle mass (e.g., many elderly, chronically ill)
• People with edema
• People with limited stature or the very tall
Weight Loss

- Refer patients to sensible diet programs (Weight Watchers, Jenny Craig, etc.)
- May require weight loss medications
  - orlistat (Xenical® or Alli®), sibutramine (Meridia®)
Waist Circumference

- Indirect measure of central adiposity, correlated with visceral fat
Visceral Fat

Obesity Types in Men and Women

Men
Central

Women
Central
Peripheral
Waist Circumference - Determination

- Locate upper hip bone and top of right iliac crest.
- Place measuring tape in a horizontal plane around the abdomen at the level of the right iliac crest.
- Ensure tape is snug but does not compress skin and is parallel to the floor.
- Measure at the end of a normal expiration.

*Circulation* 2005;112:2735-52.
A plugger’s belt size is not necessarily his waist size.
Waist Circumference - Interpretation

- High risk
  - Men ≥ 40 in
    - Use ≥ 35 inches for Asian American men
  - Women ≥ 35 in
    - Use ≥ 31 inches for Asian American women
- Adds one risk category above that defined by BMI
## Classification of Overweight and Obesity by BMI, Waist Circumference, and Associated Disease Risk

<table>
<thead>
<tr>
<th>BMI (kg/m^2)</th>
<th>Obesity</th>
<th>Disease Risk *</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Class</td>
<td>M ≤ 40</td>
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<tr>
<td>Underweight</td>
<td>&lt; 18.5</td>
<td>F ≤ 35</td>
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<tr>
<td>Normal weight</td>
<td>18.5 – 24.9</td>
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<td>Overweight</td>
<td>25-29.9</td>
<td>Increased</td>
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<tr>
<td>Extreme Obesity</td>
<td>≥ 40</td>
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</table>

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To prevent a heart attack, take one aspirin every day. Take it out for a jog, then take it to the gym, then take it for a bike ride...
Physical Inactivity, U.S. Median

- Total: 27.8
- Women: 30.8
- Men: 26
Metabolic Syndrome - Treatment

- Increasing physical activity
  - Reduces metabolic syndrome risk factors
  - Increases HDL
  - Improves cardiovascular function
- Goal
  - 30 – 60 minutes at least 5 days/week
  - 60 minutes daily is preferable
- Use pedometer and aim for 10,000 steps/day
Metabolic Syndrome
Meeting Goals for Concomitant Conditions
## JNC-7 Classification of Blood Pressure

<table>
<thead>
<tr>
<th>Category</th>
<th>Systolic BP (mm Hg)</th>
<th>Diastolic BP (mm Hg)</th>
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</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;120</td>
<td>&lt;80</td>
</tr>
<tr>
<td>Prehypertension</td>
<td>120-139</td>
<td>80-89</td>
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<tr>
<td>Stage 1 HTN</td>
<td>140-159</td>
<td>90-99</td>
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<tr>
<td>Stage 2 HTN</td>
<td>&gt;160</td>
<td>&gt;100</td>
</tr>
</tbody>
</table>

*JAMA 2003;289:2560-72.*
Metabolic Syndrome - Treatment

• Blood Pressure Goals
  • $\leq 140/80$ mm HG for patients without metabolic syndrome
  • $\leq 130/80$ mm HG in patients with metabolic syndrome/diabetes/impaired glucose tolerance

JAMA 2003:289:2560-2572
Diabetes Care 2006;29(suppl 1)
Effects of ARBs/ACEIs on DM Development

• Studies not designed for diabetes prevention
  • HOPE, PEACE, EUROPA – ACEIs decreased risk ~27%
  • LIFE - ARBs decreased risk 23%

• Prospectively designed for diabetes prevention
  • DREAM (N Engl J Med 9/15/06)
    • 18.1% with ramipril vs 19.5% with placebo
    • Different patient group than studies above
      • No heart disease or hypertension, IGT or IFG
Lifestyle Modifications for Hypertension Prevention and Management

• Weight loss
• Smoking cessation
• Increased physical activity
• Limit alcohol
  • 1 oz/day for men, ½ oz/day for women/lighter weight men
• Limit sodium intake to no more than 2.4 gm sodium or 6 gm sodium chloride per day
• Meet recommended daily intake of magnesium, potassium, and calcium
  • Emphasize increased consumption of fresh fruits, vegetables, and low-fat dairy products
Metabolic Syndrome - Treatment

- **Glucose Goals**
  - HgA₁c < 7.0%
  - Fasting and preprandial glucose 90-130 mg/dl
  - Peak postprandial < 180 mg/dl

*Diabetes Care* 2007;30:S4-41.
Interventions To Delay or Prevent Overt Type 2 Diabetes

• Intensive lifestyle changes
  • 58% ↓ risk in NIH Diabetes Prevention Program
Interventions To Delay or Prevent Overt Type 2 Diabetes

• Medications
  • Metformin (Glucophage)
    \[\downarrow \text{risk 31\% in Diabetes Prevention Program}\]
  • Thiazolidinediones (Glitazones)
    • Troglitazone \[\downarrow \text{risk 49\% in TRIPOD (high risk Hispanic women)}\]
    • Rosiglitazone (Avandia) \[\downarrow \text{risk \sim 50\% in DREAM [\uparrow CV risk]}\]
    • Pioglitazone (Actos) increases HDL and decreases TG more than rosiglitazone

Pharmacotherapy 2004;224(3):362-7
Lancet 2006;368:1096-105
Interventions To Delay or Prevent Overt Type 2 Diabetes

• Medications (continued)
  • Acarbose (Precose)
    ∀ ↓ risk 25% in STOP-NIDDM
  • ACE-I
    • Ramipril (Altace) ↓ risk 34% in HOPE
  • ARB
    • Losartan (Cozaar) ↓ risk 25% in LIFE

Pharmacotherapy 2004;224(3):362-7
# Metabolic Syndrome – Treatment

## Lipid Goals

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL Goal</th>
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<tbody>
<tr>
<td>CHD or CRE (10-year risk &gt; 20%)</td>
<td>&lt; 100 mg/dl</td>
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<td>(&lt;70 is option)</td>
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<tr>
<td>2+ Risk Factors (10 year risk &lt; 20 %)</td>
<td>&lt; 130 mg/dl</td>
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<td>(&lt;100 is option)</td>
</tr>
<tr>
<td>0 – 1 Risk Factor</td>
<td>&lt; 160 mg/dl</td>
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</table>

CRE = cardiovascular risk equivalent  
RF = risk factor

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**JAMA** 2001;285:2486-2497  
**Circulation** 2005;110:227-239
Metabolic Syndrome – Treatment

Lipid Goals

<table>
<thead>
<tr>
<th>Category</th>
<th>Goals</th>
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<tbody>
<tr>
<td>HDL*</td>
<td>&gt; 40 mg/dl (men)</td>
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<td>&gt; 50 mg/dl (women)</td>
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<tr>
<td>Triglycerides</td>
<td>&lt; 150 mg/dl</td>
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*American Diabetes Association
NCEP ATP III – HDL > 40 for both genders
AHA – HDL > 40 for men, > 45 for women

*Diabetes Care 2006;29(suppl 1)
Heart Protection Study

- 5 year study comparing simvastatin (Zocor) 40 mg qd vs vitamins (600 mg E, 250 mg C, 20 mg beta-carotene) vs placebo
- Risk of cardiovascular events decreased significantly by statin irrespective of baseline LDL in
  - Men
  - Diabetics
  - Women
  - Over 75
  - Prior stroke, MI, or PVD

∀ ↓ risk of vascular events 13%, stroke 25%, and coronary or noncoronary revascularization 24%

Antioxidant Vitamins

- Observational studies – people with high intake of carotene, ascorbic acid, and tocopherol (diet and/or supplements) have ↓ risk of MI and stroke
- Randomized trials – No consistent benefit as single vitamin or combination in primary or secondary prevention
How do Statins Decrease Risk of CVD in Patients with Low or Normal LDL?

• Pleotropic effects
  • Anti-inflammatory effects that decreases C-reactive protein (CRP)
• Decreased insulin resistance
• Target goals not low enough

Circulation 1999;100:230-235
Circulation 2001;103:357-382
Atherosclerosis 2000;150:121-27
Getting Patients to Their Lipid Goal

• LDL-C lowering
  • First choice: statin
  • Second choice: ezetimibe, niacin, fibrate
  • May require combination therapy
  • Statins and fibrates have been shown to reduce CHD risk in patients with metabolic syndrome

Pharmacotherapy 2006;26:1S-45S.
Getting Patients to Their Lipid Goal

- **HDL-C raising**
  - Behavior interventions (wt loss, increased physical activity, smoking cessation)
  - Glycemic control
  - Niacin or fibrate

- **Triglyceride lowering**
  - Glycemic control first priority
  - Fibrate or niacin
Metabolic Syndrome - Treatment

- Prothrombotic state - Aspirin
  - 75-325 mg if CHD or CRE or 10 yr risk for CHD ≥ 10% (women and men)
  - 81 mg in men for primary prevention if 10-year risk for CHD ≥ 10% (AHA)
  - 81 mg in women for primary prevention if ≥65 & maybe if <65 (AHA)
  - 75-162 mg for patients with diabetes >40 or >20 with any other CVD risk factors (ADA + AHA)
  - 81 mg if >50 with at least 1 risk factor for CVD (Guidelines for Antithrombotic Therapy for the Prevention and Treatment of Thrombosis)
Metabolic Syndrome - Treatment

- Proinflammatory state
  - No specific therapies beyond lifestyle changes are recommended
  - Weight loss & lipid lowering agents (statins, fibrates, niacin) will reduce hs-CRP

*Circulation* 2005;112:2735-52.
Pharmacist’s Role

• Identify and screen patients who potentially have metabolic syndrome
• Refer for appropriate diagnosis and treatment
• Reinforce treatment plan and enhance adherence
• Offer lifestyle modification program
Case Study

- 47 year old male on no medications
- BMI 35, Waist 42 inches
- BP 136/86
- Family history
  - Father died of MI at 59
  - Mother, 64, has HTN and high cholesterol
- Fasting laboratory values
  - TC = 195 mg/dl
  - TG = 148 mg/dl
  - LDL = 127 mg/dl
  - HDL = 38 mg/dl
  - Glucose = 116 mg/dl
Case Study

- What should be his goals?
- What therapies should he be started on?
Case Study
Metabolic Syndrome Conclusion

- Patients with metabolic syndrome are at grave risk for heart disease
- A better name is cardiometabolic syndrome
- Weight loss and physical activity are KEY to treatment
- Each condition present should be treated to accepted goals
- Pharmacotherapy to treat conditions and prevent development of type 2 diabetes may include an ACE-I or ARB, statin \( \pm \) other lipid lowering agents, metformin or TZD, and aspirin