Metabolic Syndrome

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Objectives

• Be able to outline the pathophysiology of the metabolic syndrome
• Be able to list diagnostic criteria for the metabolic syndrome
• Be familiar with laboratory tests useful for the diagnosis and monitoring of the metabolic syndrome
Outline

• Introduction
• Pathophysiology
• Laboratory testing
• Chronic kidney disease
• Exercise
• Non-alcoholic fatty liver disease
• Conclusions
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<tr>
<th>Children/Adolescents</th>
<th>Baby Boomers</th>
<th>Geriatrics</th>
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<td>Metabolic syndrome</td>
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<td>Gout</td>
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<td>Chronic liver disease(s)</td>
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<td>Dementia/Alzheimer</td>
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<td>Pain perception</td>
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<td>Overactive bladder</td>
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<td>Vitamin B12 deficiency</td>
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<td>Acute alcoholism</td>
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<td>Incontinence</td>
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Metabolic Syndrome

• What is it?
  – Constellation of clinical and laboratory findings resulting from central obesity and insulin resistance
• aka cardiometabolic syndrome, dysmetabolic syndrome X, syndrome X
• 47 to 60 million Americans have metabolic syndrome
• At increased risk for:
  – Diabetes mellitus
  – Coronary heart disease
  – Stroke
## Diagnostic Criteria

<table>
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<tr>
<th>Criterion</th>
<th>NCEP ATP III</th>
<th>WHO 1999</th>
<th>IDF 2005</th>
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<tbody>
<tr>
<td>Central obesity</td>
<td>W &gt;40 in M</td>
<td>W:H &gt;0.9 M</td>
<td>&gt;37 in M</td>
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<td>W &gt;35 in F</td>
<td>W:H &gt;0.85 F</td>
<td>&gt;31 in F</td>
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<tr>
<td>Fasting glucose</td>
<td>&gt;100 mg/dL</td>
<td>&gt;=120 mg/dL</td>
<td>&gt;100 mg/dL</td>
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<tr>
<td>Blood pressure</td>
<td>&gt;130/85 or Rx</td>
<td>&gt;140/90 or Rx</td>
<td>&gt;130/85 or Rx</td>
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<tr>
<td>Fasting TGs</td>
<td>&gt;=150 mg/dL</td>
<td>&gt;=150 mg/dL</td>
<td>&gt;=150 mg/dL</td>
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<tr>
<td>HDL-C</td>
<td>&lt;40 mg/dL M</td>
<td>&lt;=35 mg/dL M</td>
<td>&lt;40 mg/dL M</td>
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<td>&lt;50 mg/dL F</td>
<td>&lt;=39 mg/dL F</td>
<td>&lt;50 mg/dL F</td>
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<td>WHO microalbuminuria</td>
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Controversy about Metabolic Syndrome

- AHA contends recognizing metabolic syndrome will help clinicians prevent CVD
- ADA contends metabolic syndrome does not exist as a medically definable syndrome
  - Clinical treatment of syndrome is no different than treating individual components
  - Each risk factor has different degrees, everyone with metabolic syndrome does not have the same risk
Metabolic Syndrome as Predictor of CVD

• In the Framingham study, metabolic syndrome alone predicted 25% of all new onset CVD
• In the absence of diabetes, metabolic syndrome did not raise 10 year risk of CVD to >20%--the threshold for ATP III’s CHD risk equivalent
• Ten year risk in men with metabolic syndrome was 10-20%
• Ten year risk for women was lower but they were younger
Factors Contributing to Cardiometabolic Risk

Obesity in the US

US adults 20-74 y.o. who are obese, %

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<td>20</td>
<td>30</td>
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Obesity and Abnormal Body Fat Distribution

• Obesity epidemic mainly responsible for rising prevalence of metabolic syndrome

• Obesity contributes to
  – Hypertension
  – Elevated serum cholesterol (VLDL)
  – Decreased serum HDL-cholesterol
  – Hyperglycemia
Abdominal Obesity

• Form of obesity most strongly associated with metabolic syndrome and CVD risk
• Presents clinically as increased waist circumference
  – BMI can also be used, but may be less specific
  – Weight lifters have increased BMI, but usually not abdominal obesity
Products of Excess Adipose Tissue

• Non-esterified fatty acids (NEFA)
  – Overloads muscle and liver with lipid, enhances insulin resistance

• PAI-1
  – Contributes to pro-thrombotic state

• Adiponectin
  – Low adiponectin (seen in obesity) correlate with worsening of metabolic risk factors

• Pro-inflammatory cytokines
  – Increase CRP, fibrinogen, and other acute phase reactants
Energy imbalance

Excess dietary carbohydrates

Excess dietary fats / chylomicrons

Excess dietary carbohydrates

Adipocyte

Hypertrophy & Hyperplasia

Cell Dysfunction

See Figure 2

Beta cell

ER & oxidative stress

Insulin resistance

Apoptosis

Adipokines

Free Fatty Acids

Inflammatory Mediators

Skeletal muscle

Cardiac muscle

Endothelium

Hepatocyte

Lipogenesis

Steatohepatitis

Insulin resistance

Insulin Resistance

• Present in majority of people with metabolic syndrome
• Correlates with CVD risk
• Mechanisms underlying link to CVD uncertain
• Insulin resistance may manifest as glucose intolerance
• Many investigators place a greater priority on insulin resistance than obesity
• Insulin resistance increases with increasing body fat content
• A broad range of insulin sensitivities exist at any given level of body fat
Insulin Resistance and BMI

- Body mass index (BMI) $>30 \text{ kg/m}^2$ is associated with postprandial hyperinsulinemia
- BMI 25 to 29.9 show spectrum of insulin resistance
- BMI $<25 \text{ kg/m}^2$ is associated with insulin resistance in some populations (South Asians)
- High prevalence of DM and premature CVD in South Asians associated with primary insulin resistance
- Weight gain enhances insulin resistance in primary insulin resistance
Consequences of Hyperinsulinism

- Premature atherosclerosis
- Elevated blood pressure
- Hyperandrogenism—ovarian androgen secretion
- Hyperuricemia
- Major cause of PCOS
- Dylipidemia
  - Hypertriglyceridemia
  - Low HDL-cholesterol
  - Increased LDL particle number
- Fatty infiltration of liver (NAFL → NASH → cirrhosis → HCC)
Metabolic Syndrome Predicts Diabetes

- Risk of new onset diabetes mellitus examined in Framingham cohort
- In men and women the presence of metabolic syndrome was highly predictive
- Nearly half of population attributable risk for diabetes was explained by the presence of ATP III metabolic syndrome
Prevention/Delay of Type 2 DM

• Patients with IFG or IGT
  – Weight loss of 5-7% body weight can prevent DM
  – Increased physical activity 150 min/week walking

• In addition to lifestyle counseling, metformin may be considered if both
  – Combined IFG and IGT plus other risk factors
  – Obese (BMI >30 kg/m²) and under 60 yrs old
Atherogenic Dyslipidemia

- Elevated fasting triglycerides concentration
- Low HDL-cholesterol concentration
- Increased VLDL & remnant lipoprotein concentrations
- Increased apolipoprotein B concentration
- Increased number of LDL particles
- Small LDL particles
- Small HDL particles
Lipoprotein Metabolism in Metabolic Syndrome

Elevated Blood Pressure

- Associated with obesity
- Commonly occurs in insulin resistance
- Multifactorial in origin
- Arterial stiffness contributes to systolic hypertension in the elderly
Pro-inflammatory State

• Recognized clinically as elevated C-reactive protein (CRP)
• Commonly present in metabolic syndrome
• One cause is obesity—adipose tissue release IL-6 which stimulates the liver to produce CRP
JUPITER Trial

- LDL-C < 130 mg/dL
- CRP ≥ 2 mg/L
- Randomized to a statin or placebo
- Followed for 3 years
- Trial ended early due to benefits of statins in this group
  - Decreased rate of first major cardiovascular event
  - Decreased rate of death from any cause

Ridker PM et al. NEJM 2008;359:2195-2207.
Hs-CRP and Metabolic Syndrome

- 14,719 women followed for 8 years, 24% had MS
- Outcomes—MI, CVA, CABG/PTCA, cardiac death
- CRP strongly correlated with number of MS criteria
  - 0.7, 1.1, 1.9, 3.0, 3.9, 5.8 mg/L median CRP for 0-5 MS criteria
- At all levels of MS severity, CRP added information
  - CRP <3 mg/L 3.4 per 1000 incidence of event
  - CRP >3 mg/L 5.9 per 1000 incidence of event
- CRP increases PAI-1 expression in aortic endothelial cells
Useful Laboratory Tests

- Apolipoprotein B
- Creatinine
- Fasting triglycerides
- Fasting glucose
- HDL-cholesterol
- Hs-CRP
- LDL-cholesterol
- LDL particle number
- Non-HDL cholesterol
- Urine albumin
Lipoprotein Subclasses and MS

- Subjects with insulin resistance/metabolic syndrome tend to have dyslipidemia:
  - Increased large VLDL particle concentrations
  - Increased small LDL particle concentrations
  - Decreased large HDL particle concentrations
- Small dense LDL particles (B phenotype) is associated with increased cardiovascular risk
- The apolipoprotein B (apo B) concentration reflects number of LDL particles
- Treatments targeting this dyslipidemia may be beneficial
Lipoprotein Management

- **LDL-cholesterol**
- **LDL particle number**
  - Better predictor than LDL-C
  - More data needed across ethnicities and ages
- **Non-HDL-cholesterol**
  - Better predictor than LDL-C
  - Useful in hypertriglyceridemia as secondary target
- **ApoB-100**
  - Single molecule in each atherogenic particle
  - Better predictor than LDL-C
## Lipid Treatment Goals

<table>
<thead>
<tr>
<th>Scenario</th>
<th>LDL-C (mg/dL)</th>
<th>Non-HDL-C (mg/dL)</th>
<th>ApoB (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Known CVD or 2) DM plus one or more additional CVD risk factors</td>
<td>&lt;70</td>
<td>&lt;100</td>
<td>&lt;80</td>
</tr>
<tr>
<td>1) No DM or known CVD but 2 or more additional risk factors or 2) DM but no other major CVD risk factors</td>
<td>&lt;100</td>
<td>&lt;130</td>
<td>&lt;90</td>
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Chronic Kidney Disease

- The persistent and usually progressive reduction in glomerular filtration rate (GFR less than 60 mL/min/1.73 m²), and/or
- Albuminuria (more than 30 mg of urinary albumin per gram of urinary creatinine)
Cardiovascular Disease is Linked to CKD

• Annual mortality from CVD is increased 10 - 100 times with kidney failure
• Risk of CVD is increased 1.4 - 2.05 times with creatinine >1.4 - 1.5 mg/dL
• Risk of CVD is increased 1.5 - 3.5 times with microalbuminuria >30 mg/g
Who is at Risk for Chronic Kidney Disease?

• Diabetes and high blood pressure are the leading causes of kidney failure.
• Individuals with a family history of kidney failure are also at risk.
• Chronic kidney disease may also result from:
  – Hereditary factors, such as polycystic kidney disease (PKD)
  – A direct and forceful blow to the kidneys
  – Prolonged consumption of some over-the-counter painkillers that combine aspirin, acetaminophen, and other medicines such as ibuprofen
Kidney Disease Prevalence Increases with Age

Limitations of MDRD eGFR

• Validated for adults 18-70 years of age
• Not validated for hospitalized patients
• Not as accurate for eGFR >60 mL/min/1.73 m²
• Not as accurate when patient's basal creatinine production is very abnormal
  – Patients of extreme body size or muscle mass (e.g., obese, severely malnourished, amputees, paraplegics or other muscle-wasting diseases)
  – Unusual dietary intake (e.g., vegetarian, creatine supplements).
Urinary Albumin/Creatinine Ratio

- A single cutoff (30mg/g) is used
- Age, gender, and race may affect cutoff
- No uniformity in sample type
  - First morning void vs. true random
  - Diurnal, postural, exercise influences
  - Sample handling
    - Non-specific binding to collection container
    - Degradation during storage and freeze-thaw
Who should be Tested for CKD?

• Microalbumin and eGFR
  – All individuals with hypertension—at diagnosis and every 3 years if normal
  – Diabetes mellitus—every year
  – Family history of CKD, every 3 years if normal
  – Those with CVD or increased risk of CVD

• eGFR
  – All individual >65 years old
Exercise and the Metabolic Syndrome

• Regular exercise can help prevent diabetes mellitus
• Exercise can:
  – Lower blood glucose
  – Improve insulin action
  – Contribute to weight loss
  – Reduce risk for cardiovascular disease
• Sedentary lifestyles linked to 23% of deaths from heart disease and diabetes mellitus
• 30 minutes/day of walking can be beneficial
• Strength and endurance training can both be beneficial
Effects of Lifestyle Modifications on Metabolic Syndrome

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<tr>
<th>Metabolic Syndrome Component</th>
<th>Effect of Regular Exercise$^a$</th>
<th>Effect of Chronic Caloric Restriction$^b$</th>
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<tr>
<td>Waist circumference, cm (%)</td>
<td>−3 to −7 (6)</td>
<td>−4 to −7 (−6)</td>
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<td>Triglycerides, mmol/L (%)</td>
<td>−0.21 (−12)</td>
<td>−0.12 (−6)</td>
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<td>HDL cholesterol, mmol/L (%)</td>
<td>+0.05 (+4)</td>
<td>+0.07 (+6)</td>
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<td>Fasting plasma glucose, mM (%)</td>
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<tr>
<td>Nondiabetic subjects</td>
<td>Negligible</td>
<td>Negligible</td>
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<tr>
<td>Diabetic subjects</td>
<td>−1.5 (−15)</td>
<td>−1.2 (−15)</td>
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<td>Blood pressure, mmHg</td>
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<td>Systolic</td>
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<td>Diastolic</td>
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Moderate intensity exercise 3-5 days/wk, 30-60 min/day
Modest daily caloric restriction (500-700kcal)

Non-alcoholic Fatty Liver Disease (NAFLD)

- Nearly one third of American adults
- 70% of patients with diabetes mellitus
- Central adiposity and insulin resistance contribute in both men and women
- Can progress to non-alcoholic steatohepatitis, cirrhosis, fibrosis, and hepatocellular carcinoma
Diagnosis of NAFLD

• LFTs
  – Mild elevations of ALT and GGT
• Ultrasound
• CT
• MRI
• Liver biopsy—definitive diagnostic test
Conclusions

• CVD is the primary clinical outcome of metabolic syndrome
• ATP III criteria identify patients at increased risk for CVD
• Metabolic syndrome confers increased risk for DM
• The liver plays a central role in the metabolic syndrome
• Therapeutic lifestyle changes with emphasis on exercise and weight reduction constitute first line therapy
General References

- NKDEP web site: nkdep.nih.gov/