Disclosures: None

Financial Disclosures/Unapproved Use

- I have no financial relationships with a commercial entity that is relevant to the content of this presentation.
- I will/will not reference unlabeled or unapproved uses of drugs or other products.
Main Points

1. Metabolic syndrome (MetS) is useful clinical phenotype, but current definitions have limitations.
2. MetS is predominantly a disease of lifestyle.
3. Early detection of subclinical atherosclerosis can determine need for pharmacotherapy.
4. A pharmacologic strategy can be tailored to patients with disordered metabolism.

Table 2. Prevalence of metabolic syndrome in Asian countries

<table>
<thead>
<tr>
<th>Country</th>
<th>Prevalence of metabolic syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>India</td>
<td>30-40%</td>
</tr>
<tr>
<td>Thailand</td>
<td>13-19%</td>
</tr>
<tr>
<td>Singapore</td>
<td>13%</td>
</tr>
<tr>
<td>China</td>
<td>10-15%</td>
</tr>
<tr>
<td>Japan</td>
<td>8-15%</td>
</tr>
</tbody>
</table>

Is the metabolic syndrome more than the sum of its parts?

**Multiplicative risk:** risk rises geometrically with multiple risk factors

**Hidden (unmeasured) risk factors:** high apo B; small LDL; prothrombotic & proinflammatory states; endothelial dysfunction, insulin resistance

**Progression:** MetS is a progressive condition

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Steady Increase in Anticipated HF Cases in Coming Decades

Biggest Contributors:
- **Aging population:**
- **Increased HF survival:**
- **Obesity epidemic:** approximately 25-30% of HF cases related to overweight/obesity

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Is HFpEF or HFrEF the Predominant Form of HF Among Those with Obesity?

HFpEF incidence greater in obesity:

Combination of Obesity and Elevated hs-cTnT Associated with Markedly Increased Risk of Incident HF

The Metabolic Syndrome IS:

A useful clinical phenotype for explaining:

- High triglycerides
- Low HDL-C
- Elevated hsCRP
- HbA1c >6%
The Metabolic Syndrome IS:

A useful clinical phenotype for communicating:

- Very high risk for diabetes
- Higher short term risk for CVD
- Very high lifetime risk for CVD
- Mechanism of risk – lifestyle and genetics
- Risk beyond expected by traditional risk factors

Table 4. Race/ethnic-specific cutpoints for abdominal obesity in the "harmonized" definition

<table>
<thead>
<tr>
<th>Population</th>
<th>Threshold for abdominal obesity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>Men</td>
</tr>
<tr>
<td>European</td>
<td>≥94 cm</td>
</tr>
<tr>
<td>Caucasian</td>
<td>≥84 cm (increased risk)</td>
</tr>
<tr>
<td>Asian (Including Japanese)</td>
<td>≥102 cm (still higher risk)</td>
</tr>
<tr>
<td>Chinese</td>
<td>≥85 cm</td>
</tr>
<tr>
<td>Middle East, Mediterraneans</td>
<td>≥84 cm</td>
</tr>
<tr>
<td>Sub-Saharan African</td>
<td>≥84 cm</td>
</tr>
<tr>
<td>Ethnic Central and South American</td>
<td>≥80 cm</td>
</tr>
</tbody>
</table>

Sperling LS et al., JACC 2015;66(9):1050-67

Staging system for MetS- A Framework
Sperling LS et al., JACC 2015;66(9):1050-67

- Identify
- Risk-stratify
- Apply evidence-based therapeutic interventions
  - **imperative that Rx decisions incorporated within context of absolute risk
Paradigm for Subtyping MetS

- At risk for multi-end-organ damage
- CV & non-CV
- Variability in end-organ involvement
- Overlap
- Target preventive / therapeutic approaches


Stages in Evolution of MetS (Therapy by Stage)
Sperling LS et al., JACC 2015;66(9):1050-67

The ABCDE Approach

- **A**: Assessment
  - Aspirin
- **B**: Blood pressure
- **C**: Cholesterol
- **D**: Diabetes Prevention
  - Diet
- **E**: Exercise
Assessment

Among lower risk individuals, metabolic syndrome may be associated with risk not accounted for by traditional risk scoring algorithms.

Risk Assessment Determines Need for Meds

Metabolic Syndrome (3+ Metabolic Risk Factors)

- All Patients
- Higher Lifetime Risk for CVD and T2DM
- Global Risk Assessment
- Higher 10-Year Risk for CVD

Risk Assessment Determines Need for Meds

- Lifestyle Therapies
- Drug Therapies

Imaging with CAC or CIMT for Risk Stratification

CHD Risk in DM and MetS depends on the extent of subclinical disease present: Higher CAC scores = ↑ risk for CVD events.

CAC screening is a Class Ic ACCF/AHA guideline recommendation for screening in asymptomatic people with DM.

Aspirin Therapy

Recent evidence mandates an individualized approach after risk assessment

Aspirin Evidence: Primary Prevention

Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD) Study

2,539 diabetic patients without known coronary artery disease randomized to aspirin (81-100 mg) or placebo for a median of 4.7 years.

Aspirin does not reduce the risk of adverse CV events in diabetics

Ogawa H et al. JAMA 2008;300:2134-41

Risk/Benefits of ASA According to CAC

* Represents number needed to harm for a major bleeding event

Miedema et al. ASA and CAC – Circ. Quality 2014
Blood Pressure

Choice of Initial Agent – ACE or ARB
Add-on Therapy – Consider Amlodipine
Target Blood Pressure - <=140/90

JNC VII Guidelines: Lifestyle Modifications for BP Control

<table>
<thead>
<tr>
<th>Modification</th>
<th>Recommendation</th>
<th>Approximate SBP Reduction Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight reduction</td>
<td>Maintain normal body weight (BMI=18.5-25)</td>
<td>5-20 mmHg/10 kg weight lost</td>
</tr>
<tr>
<td>DASH eating plan</td>
<td>Diet rich in fruits, vegetables, low fat dairy and reduced in fat</td>
<td>8-14 mmHg</td>
</tr>
<tr>
<td>Restrict sodium intake</td>
<td>&lt;2.4 grams of sodium per day</td>
<td>2-8 mmHg</td>
</tr>
<tr>
<td>Physical activity</td>
<td>Regular aerobic exercise for at least 30 minutes most days of the week</td>
<td>4-10 mmHg</td>
</tr>
<tr>
<td>Moderate alcohol</td>
<td>&lt;2 drinks/day for men and &lt;=1 drink/day for women</td>
<td>2-4 mmHg</td>
</tr>
</tbody>
</table>

BMI=body mass index, SBP=systolic blood pressure

Chobanian AV et al. JAMA 2003;289:2560-2572

Risk of Developing Diabetes Mellitus Among Different Antihypertensive Agents

Systematic review of 22 clinical trials evaluating 143,153 patients without DM randomized to an antihypertensive agent

Treatment with an ARB or ACE inhibitor carries the lowest risk of developing DM, whereas treatment with a diuretic or β-blocker carries the highest risk.

ACE=Angiotensin converting enzyme, ARB=Angiotensin receptor blocker, DM=Diabetes mellitus

In patients aged ≥18 years with diabetes, initiate pharmacologic treatment at systolic BP ≥140mmHg or diastolic BP ≥90mmHg. Treat to a goal systolic BP <140mmHg and goal diastolic BP <90mmHg. (Expert Opinion–Grade E)

For adults with diabetes aim for the same BP goals as in the general population. Treat if BP >140/90; Aim for <140/90

ADA. Diabetes Care 2016 Jan; 39(Supplement 1): S4-S5.
AACE 2016 recommends <130/80 mmHg for most DM, but as low as <120/80 mmHg if it can be achieved safely (Garber et al. Endocr Prac 2016)

Cholesterol

Primary Target: LDL-C
Secondary Target: non-HDL-C

Importance of Non-HDL-C

(all apolipoprotein B-containing particles)

Fibrates in Atherogenic Dyslipidemia

Fibrates have selective benefit for atherogenic dyslipidemia

2013 ACC/AHA Cholesterol Guideline Recommendations for Adults with Diabetes

- Adults aged 40-75 years without ASCVD but with DM + LDL-C 70-189 mg/dL
- If 10-y ASCVD risk ≥ 7.5%
- Risk decision uncertain?
  - Family history of premature ASCVD
  - Hs-CRP ≥ 2.0 mg/L
  - ↑ life8me risk of ASCVD
  - CAC score ≥300 Agaston units
  - LDL-C ≥160 mg/dL
  - ABI <0.9

ESC, NLA, AACE still recommend targets, eg <100 mg/dl for DM w/o RF, <70 mg/dl for DM with RF or ASCVD

Diabetes Prevention

Lifestyle Therapy!!
Consider Metformin
Pre-diabetic Conditions: Benefit of Lifestyle Modification

Diabetes Prevention Program (DPP)
3,234 patients with elevated fasting and post-load glucose levels randomized to placebo, metformin (850 mg bid), or lifestyle modification* for 3 years

Lifestyle modification reduces the risk of developing DM

*Includes 7% weight loss and at least 150 minutes of physical activity per week


Diet

1. Weight Loss
2. Mediterranean Diet
3. Low Glycemic Index Diet
4. No Sugared Beverages
5. Nuts for Snacks

USDA vs. Mediterranean Dietary Recommendations

USDA=United States Department of Agriculture
Mediterranean Diet & Reduction in Metabolic Syndrome

- Meta-analysis of 50 studies; 535K
- Adherence associated with 31% reduction in MS
- Protective effects
  - Waist circ: -0.4 cm
  - HDL: +1 mg/dl
  - TG: -6 mg/dl
  - Syst BP: -2.4 mm Hg
  - Diast BP: -1.6 mm Hg
  - BG: -3.9 mg/dl

Kastorini CM, et al. JACC 2011;57

Importance of Carbohydrates
Low Glycemic Index/Load Concept

USDA Nutrition Guidelines – June 2011

- 7 Key Messages
  1. Enjoy food but eat less
  2. Avoid oversized portions
  3. half plate fruits/vegs
  4. Water over sugary drinks
  5. Fat free /low-fat milk
  6. Compare sodium in foods
  7. > half grains whole
Assessments at JHWMC

**Nutrition Assessment**
- Discuss weight loss goals, expectations, & target weight
- Assess level of motivation for sustained weight control
- Discuss eating environment
- Determine meal & snack patterns; trigger foods
- Discuss individualized weight loss method

**Behavioral Assessment**
- Assess mental health concerns, family background, & onset of obesity
- Discuss ways to improve self care
- Identify triggers to overeating and unplanned eating
- Discuss/introduce barriers to action & motivation, and obstacles

Weight Loss Phase

**Quick Start / Living Light: Meal Replacement Programs**
- Highly structured / medically monitored program
- Quick Start: 6 meal replacements daily (until ~75% of target weight is lost)
- Living Light: 5 meal replacements + 1 whole food meal (once close to target wt)
- Weekly support group / Individual appointments optional.
- Gradual transition to regular food once approaching target weight.

**Individualized Meal Program**
- Accommodates individuals with soy, dairy, or gluten allergy.
- Individualized, food-based eating plan designed by client and RD
- Optional meal replacements for snacks or meals
- Attendance at weekly support group and/or regular individual clinician follow-up
- Medical evaluation & physician monitoring during dieting process is encouraged

Transition Phase

**Transitioning to a Food-Based Diet**

Lasting changes in eating habits may take 2-5 yrs. To facilitate transition from meal replacements, use small meals that mimic meal replacements’ calories & protein.

By gradually replacing each meal replacement with a food-based “meal,” a repertoire of meals is created. Over time, calories consumed can increase consistent with metabolism & physical activity level.

Through transition process, the following skills are emphasized:
- Knowledge of appropriate portion size & meal timing
- Tips & tools for making healthy food choices in most situations
- Planning/preparing healthy meals
- Nutrition label reading
Exercise

1. “Some is good, more is better”
2. Need some degree of strenuous aerobic activity
3. Pedometers for feedback & motivation

Source: Hu FB et al. JAMA 2003;289:1785-91

Reduction:
Each hour a day spent walking briskly

Increase:
Each two hours a day spent watching TV
Each two hours a day spent sitting at work

Nurse’s Health Study

Risk of obesity
Risk of DM

Exercise reduces the incidence of obesity and DM
**ABCDE Approach Summary**

<table>
<thead>
<tr>
<th>A</th>
<th>Assessment</th>
<th>Consider CAC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Aspirin</td>
<td>Most &gt;10% 10-yr ASCVD risk</td>
</tr>
<tr>
<td>B</td>
<td>Blood pressure</td>
<td>CAC&gt;100 or high % for age</td>
</tr>
<tr>
<td>C</td>
<td>Cholesterol</td>
<td>ACE-I/ARB, Amlodipine add-on</td>
</tr>
<tr>
<td></td>
<td>Diet/Weight Loss</td>
<td>Target &lt;140/90 mmHg</td>
</tr>
<tr>
<td>D</td>
<td>Exercise</td>
<td>1st LDL, 2nd non-HDL</td>
</tr>
<tr>
<td>E</td>
<td>Diabetes Prevention</td>
<td>Statin, consider ezetimibe</td>
</tr>
</tbody>
</table>

**TAKE HOME MESSAGES**

- MetS confers increased risks for CVD complications
- The wide spectrum in CVD risks, however, warrants careful CVD risk assessment in such individuals
- Lifestyle modification remains the cornerstone of efforts to prevent and reduce progression of MetS to DM & ASCVD

**Helpful Sound Bytes**

“Genetics Loads the Gun, but Environment pulls the Trigger!”
- Elliot Joslin, M.D.

“Eat less, eat smart, move more daily!”
(and quit smoking if you use tobacco)
- Neil Stone, MD
- (Heavyweight Champion of Preventive Cardiology)