Myth of Metabolic Syndrome?

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Credits
This lecture is based on materials developed by:
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Chief Medical and Scientific Officer ADA
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Touro University, Vallejo, CA
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Professor and Associate Dean Research
Texas Tech University HSC, Odessa, TX

Pre Test Question
1. Metabolic syndrome
   a. implies that insulin resistance is the core defect resulting in vascular disease
   b. addresses the epidemiology of cardiovascular and peripheral vascular disease
   c. explains ethnic disparities in the prevalence of obesity and hypertension
   d. focuses on small-dense LDL cholesterol as the major cardiovascular risk factor
Pre Test Question

2. The parameters defining metabolic syndrome
   a. include blood pressure, glucose, hsCRP, total cholesterol and obesity
   b. are used to predict cardiovascular risk only if all 5 parameters are abnormal
   c. have all been validated for sensitivity, specificity and positive predictive value
   d. have undergone multiple revisions over the last decade

Pre Test Question

3. The physician should diagnose metabolic syndrome in patients because
   a. it is the best tool to predict who will develop diabetes
   b. it remains the most accurate way to predict a second myocardial infarction
   c. it highlights those patients where lifestyle changes will prevent disease
   d. it outlines specific therapeutic choices for the management of the hyperlipidemia

History of the Metabolic Syndrome

The forerunner of MBS was described by Kylin\(^1\) in 1923 and again later by Vague\(^2\) in 1956.

What we now recognize as MBS resulted from Reaven’s synthesis of data as presented in his 1988 Banting Lecture to the ADA\(^3\). He proposed that the pathophysiology of atherosclerosis involved:

- Central obesity
- Hypertension
- Hyperlipidemia
- Glucose intolerance

New Criteria for the Diagnosis of Metabolic Syndrome: Waist Circumference + Any Two Other Parameters

<table>
<thead>
<tr>
<th>Measure</th>
<th>Cut Point</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waist circumference</td>
<td>Population &amp; country-specific ≥ 150 mg/dL</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>&lt; 40 mg/dL males</td>
</tr>
<tr>
<td>HDL-C</td>
<td>&lt; 50 mg/dL females</td>
</tr>
<tr>
<td>Blood pressure (or on Rx with Hx HTN)</td>
<td>SBP ≥130 &amp;/or DBP ≥85 mmHg</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>≥100 mg/dL</td>
</tr>
</tbody>
</table>


New Waist Circumference Thresholds for Abdominal Obesity

<table>
<thead>
<tr>
<th>Population</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian</td>
<td>≥ 94 cm</td>
<td>≥ 80 cm</td>
</tr>
<tr>
<td>Asian</td>
<td>90</td>
<td>80</td>
</tr>
<tr>
<td>European</td>
<td>102</td>
<td>88</td>
</tr>
<tr>
<td>Chinese</td>
<td>85</td>
<td>80</td>
</tr>
<tr>
<td>Japanese</td>
<td>85</td>
<td>80</td>
</tr>
<tr>
<td>Middle East</td>
<td>94</td>
<td>80</td>
</tr>
<tr>
<td>Sub-Saharan Africa</td>
<td>94</td>
<td>80</td>
</tr>
<tr>
<td>Central, S. America</td>
<td>90</td>
<td></td>
</tr>
</tbody>
</table>


IDF Consensus Definition for Metabolic Syndrome in Children and Adolescents

<table>
<thead>
<tr>
<th>Age</th>
<th>Waist</th>
<th>TG</th>
<th>HDL</th>
<th>BP</th>
<th>Glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 to &lt;10</td>
<td>&gt;90th percentile</td>
<td>Do not diagnose metabolic syndrome in children less than 10 years of age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 to &lt;16</td>
<td>&gt;90th percentile</td>
<td>&gt;150 mg/dL</td>
<td>&lt;40 mg/dL</td>
<td>&gt;130/85 mmHg</td>
<td>≥100 mg/dL</td>
</tr>
<tr>
<td>16+</td>
<td>Use Adult Criteria</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

What is the Intended Purpose for Identifying Metabolic Syndrome?

Explain the cause of atherosclerosis
Predict cardiovascular disease

Crux of the Argument

Do the components of metabolic syndrome (MBS) predict or identify persons at risk for cardiovascular disease better than other systems?

Does identification of MBS improve clinical outcomes?

Are the components of MBS greater than the sum of its parts?

Kahn et al. Diabetes Care 2005; 28:2289

Why are there arguments about Metabolic Syndrome?

Several studies did not find the MBS criteria powerful for predicting CVD and DM

Based on this, ADA and the EASD questioned if MBS was a syndrome and recommended evaluation and treatment of all CVD risk factors regardless of whether a person met criteria for MBS

1Stern et al. Diabetes Care 2004;27:2676
2Kahn et al Diabetes Care 2005;28:2289
Specific Objections to Metabolic Syndrome

ADA / EASD concerns about MBS:
- Not a syndrome
- Imprecise definitions (7 systems to date)
- Not useful predicting risk
- Uncertain pathogenesis
- CVD risk is not greater than sum of parts
- Medical value is unclear

Further, despite new definitions of MBS, none have data on the sensitivity, specificity or positive predictive value demonstrating that it is a useful diagnosis

Kahn et al. Diabetes Care 2005; 28:2289

Is Metabolic Syndrome Really a Syndrome?

Def: “A group of signs or symptoms that collectively indicate or characterize a disease, psychological disorder or other abnormal condition”

Examples of arguments that MBS is not a syndrome:
- a. Obesity and IFG (glucose 100-125 mg%) is not MBS, but are high risk for T2D and CVD
- b. ↑BP ↑FPG ↑TG ↓HDL and normal waist do not have MBS, yet the risk for DM and CVD is high
- c. Why exclude stronger markers to predict CVD such as age, LDL-C and family history?
- d. What about adiponectin, hsCRP, etc?

Questions About Waist Circumference

What is the cut point for Caucasian males 94 or 102 cm?
- females 80 or 88 cm?

What is the cut point for an European male living in Sub Saharan Africa?

What is the cut point of persons of mixed ethnicity?

Why stipulate waist circumference as a prerequisite for diagnosing MBS?
- It is not true that waist circumference accurately predicts insulin resistance
- It is not true that insulin resistance is the underlying defect leading to CVD.
Question

If waist circumference is to identify insulin resistance, and problems arise trying to define an abnormal waist in different people, why not just use the Body Mass Index (BMI) and simplify?

How Well Does Metabolic Syndrome Predict Insulin Resistance?

The data from four studies (using ATP-III criteria for MBS) indicate that the value of MBS to predict insulin resistance is ~equal to flipping a coin. That is, many persons with insulin resistance will be missed.

<table>
<thead>
<tr>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV%</th>
</tr>
</thead>
<tbody>
<tr>
<td>46</td>
<td>93</td>
<td>76(^1)</td>
</tr>
<tr>
<td>20-50</td>
<td>92</td>
<td>56(^2)</td>
</tr>
<tr>
<td>52</td>
<td>85</td>
<td>78(^3)</td>
</tr>
<tr>
<td>42</td>
<td>94</td>
<td>72(^4)</td>
</tr>
</tbody>
</table>

\(^1\)Cheal et al. Diabetes 2004;53:1195
\(^2\)Liao et al. Diabetes Care 2003;27:978
\(^3\)McLaughlin et al. Ann Intern Med 2003;139:802
\(^4\)Sierra-Johnson et al. Diabetes Care 2006;29:668

How Well Does Metabolic Syndrome Predict Diabetes?

How Well Does Metabolic Syndrome Predict Cardiovascular Events?

No one doubts that MBS has a positive relationship with CV events, but here’s the real question:
Is the risk conferred by each component of MBS synergistic or merely additive?
Or, as Dr. Kahn asks: “Is the whole greater than the sum of its parts.”

(MRFIT Data)

<table>
<thead>
<tr>
<th>Cardiovascular Mortality</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 component of MBS</td>
<td>1.09</td>
</tr>
<tr>
<td>2 components of MBS</td>
<td>1.29</td>
</tr>
<tr>
<td>3 components of MBS</td>
<td>1.51</td>
</tr>
<tr>
<td>4 components of MBS</td>
<td>1.98</td>
</tr>
<tr>
<td>5 components of MBS</td>
<td>2.98</td>
</tr>
</tbody>
</table>

Eberly LE et al. Diabetes Care 2006;29:123

(British Women’s Heart & Health Study)

<table>
<thead>
<tr>
<th>Cardiovascular Disease</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>MBS</td>
<td>1.32</td>
</tr>
<tr>
<td>BP &gt;130/85 or on Rx</td>
<td>2.09</td>
</tr>
<tr>
<td>BMI &gt;30</td>
<td>1.31</td>
</tr>
</tbody>
</table>

Lawlor DA, et al. 2006;Diabetologia 49:41
How Well Does Metabolic Syndrome Predict Cardiovascular Events?  
(San Antonio Heart Study)

<table>
<thead>
<tr>
<th>Cardiovascular Disease</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>MBS</td>
<td>1.56</td>
</tr>
<tr>
<td>MBS, No Diabetes</td>
<td>1.11</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.63</td>
</tr>
</tbody>
</table>

Stern MP et al. Atheroscler 2005;6(suppl):3

What is the Contribution of Metabolic Syndrome to CVD Risk?  
Let's compare 2 people, one with and one without MBS. Calculate CVD risk using a Framingham score.

<table>
<thead>
<tr>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>45</td>
</tr>
<tr>
<td>BMI</td>
<td>30</td>
</tr>
<tr>
<td>FPG</td>
<td>115</td>
</tr>
<tr>
<td>SBP</td>
<td>88</td>
</tr>
<tr>
<td>TG</td>
<td>160</td>
</tr>
<tr>
<td>HDL</td>
<td>65</td>
</tr>
<tr>
<td>LDL</td>
<td>125</td>
</tr>
<tr>
<td>Smoke</td>
<td>Yes</td>
</tr>
</tbody>
</table>

MBS Yes (4/5) No

10 y CVD Risk
<1% (10 points) >30% (10 points)

Traditional CVD Risk Assessment ATP III

Smoker
HTN (≥140/90 or on BP medication)
Low HDL (<40 mg/dL)
Family Hx premature CHD
First degree male relative <55 y
First degree female relative <65 y
Age Men ≥45 y
Women ≥55 y

If 2 or more risk factors are identified, a risk score is calculated, 10 year risk is assigned and therapy is based on the risk score.

### Total Age (years) Cholesterol (mg/dL) 20-39 40-49 50-59 60-69 70-79

- **<160** 0 0 0 0 0
- **160-199** 4 3 2 1 0
- **200-239** 8 6 4 2 0
- **240-279** 11 8 5 2 1
- **≥280** 13 10 7 4 2

### Cigarette Smoking

- **Nonsmoker** 0 0 0 0 0
- **Smoker** 9 7 4 2 1

### Age Points

- **20-34** -7
- **35-39** -3
- **40-44** 0
- **45-49** 3
- **50-54** 6
- **55-59** 8
- **60-64** 10
- **65-69** 11
- **70-74** 14
- **75-79** 16

### CHD Risk Points

- **<9** 0
- **9** 1
- **10** 1
- **11** 1
- **12** 1
- **13** 2
- **14** 2
- **15** 3
- **16** 4
- **17** 5
- **18** 6
- **19** 8
- **20** 11
- **21** 14
- **22** 17
- **23** 20
- **≥24** ≥30

### Systolic Blood Pressure

- **Untreated**
  - **<120** 0
  - **120-129** 0
  - **130-139** 1
  - **140-149** 2
  - **≥150** 3
- **Treated**
  - **<120** 0
  - **120-129** 0
  - **130-139** 1
  - **140-149** 2
  - **≥150** 3

### HDL-C (mg/dL)

- **Points**
  - **>60** -1
  - **50-59** 0
  - **40-49** 1
  - **<40** 2

### Score = 10

- **Risk (%)**
  - **<10** ≤1%
  - **10** 1%
  - **11** 1%
  - **12** 1%
  - **13** 2%
  - **14** 2%
  - **15** 3%
  - **16** 4%
  - **17** 5%
  - **18** 6%
  - **19** 8%
  - **20** 11%
  - **21** 14%
  - **22** 17%
  - **23** 20%
  - **24** 27%
  - **25** 30%

### LDL-C goal:

- **<130 mg/dL**
- **<100 mg/dL**

---

**Framingham Score for 45 y Female**

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-34</td>
<td>-9</td>
</tr>
<tr>
<td>35-39</td>
<td>-4</td>
</tr>
<tr>
<td>40-44</td>
<td>0</td>
</tr>
<tr>
<td>45-49</td>
<td>3</td>
</tr>
<tr>
<td>50-54</td>
<td>6</td>
</tr>
<tr>
<td>55-59</td>
<td>8</td>
</tr>
<tr>
<td>60-64</td>
<td>10</td>
</tr>
<tr>
<td>65-69</td>
<td>11</td>
</tr>
<tr>
<td>70-74</td>
<td>14</td>
</tr>
<tr>
<td>75-79</td>
<td>16</td>
</tr>
</tbody>
</table>

### CHD Risk Points

- **<9** 0
- **9** 1
- **10** 1
- **11** 1
- **12** 1
- **13** 2
- **14** 2
- **15** 3
- **16** 4
- **17** 5
- **18** 6
- **19** 8
- **20** 11
- **21** 14
- **22** 17
- **23** 20
- **≥24** ≥30

### Systolic Blood Pressure

- **Untreated**
  - **<120** 0
  - **120-129** 0
  - **130-139** 1
  - **140-149** 2
  - **≥150** 3
- **Treated**
  - **<120** 0
  - **120-129** 0
  - **130-139** 1
  - **140-149** 2
  - **≥150** 3

### HDL-C (mg/dL)

- **Points**
  - **>60** -1
  - **50-59** 0
  - **40-49** 1
  - **<40** 2

### Score = 17

- **Risk (%)**
  - **<10** ≤1%
  - **10** 1%
  - **11** 1%
  - **12** 1%
  - **13** 2%
  - **14** 2%
  - **15** 3%
  - **16** 4%
  - **17** 5%
  - **18** 6%
  - **19** 8%
  - **20** 11%
  - **21** 14%
  - **22** 17%
  - **23** 20%
  - **24** 27%
  - **25** 30%

### LDL-C goal:

- **<130 mg/dL**
- **<100 mg/dL**

---

**Why Does Metabolic Syndrome Not Contribute More to Determining CVD Risk?**

All the components of MBS carry the same degree of risk, where as:

- The traditional risk factors contribute varying amounts of risk depending on age, severity of hyperlipidemia and hypertension
- Traditional risk factors include other high-impact risk parameters
  - Age, Sex, Ethnicity, Family history, Smoking, Exercise, Medical history

1 in the extreme, all our systems become meaningless as age advances
Medical Value for Diagnosing Metabolic Syndrome?

Presence or absence of MBS does not change therapy and does not guide treatment decisions for blood pressure, lipids and glucose

If you want to predict diabetes: Measure glucose
If you want to predict CVD: Measure LDL-C or Count risk factors or Use a risk calculator
If you want to identify obesity: Measure waist or Calculate BMI

Consider this: Smoking alone predicts CVD as well as all 5 components of MBS!

Is There Any Value to Diagnosing Metabolic Syndrome?

Time to reverse gears and show you something really cool!

I’m going to present a case and illustrate the importance of diagnosing metabolic syndrome

A 54 year old female presents with chest pain and fatigue

Patient complains of fatigue for several months and sharp intermittent chest pains with or without exertion

Pain Entire chest wall
No radiation
Lasts seconds to ~1 hour

Nausea With or without chest pain
Symptoms Worse over the past month
Traditional CHD Risk Factors

| Smoking       | 1 pack per day | PMHx | No HTN, DM, Hyperlipidemia |
| Menopause     | 3 yrs ago, No HRT | Family Hx | Father: MI age 53 |
|               |                |       | Mother: T2DM               |
| PE            | Ht 65" Wt 161 lbs | BP 138/88 |
| BMI           | 29 Waist 36"    | HR 86  |
| Lab           | TC 210 LDL 128  | HDL 42 |
|               | FPG 120         | TG 200 |

Traditional Risk Assessment

(Patient’s LDLc = 128 mg/dL)

<table>
<thead>
<tr>
<th>Framingham</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 54</td>
<td>6</td>
</tr>
<tr>
<td>TC 210</td>
<td>4</td>
</tr>
<tr>
<td>HDL 42</td>
<td>1</td>
</tr>
<tr>
<td>BP 138/88</td>
<td>2</td>
</tr>
<tr>
<td>Smoker</td>
<td>4</td>
</tr>
<tr>
<td>TOTAL</td>
<td>17</td>
</tr>
</tbody>
</table>

10 year risk: 5% = LDL-C goal <160 mg/dL

The patient is already at-goal for LDL-C according to the Framingham score

A Stress Test Is Performed

Patient reaches 85% maximal heart rate @ 6 minutes, modified Bruce protocol

Test stopped due to SOB & fatigue

No chest pain occurred

At maximum exertion, 0.4 mm ST segment elevation seen in the inferior leads

Thallium scan reveals equivocal ischemia in the inferior wall
A Heart Catheterization Is Performed

- Normal ejection fraction
- No wall abnormalities
- Arteriography shows no significant obstruction

The test is interpreted as negative for significant coronary disease and she is returned to your care.

The patient was treated according to the ATP III guidelines: Total lifestyle changes.

So, What Went Wrong?

3 weeks later the patient was admitted to the hospital for a transmural inferior wall MI.

The heart catheterization was repeated with IVUS and extensive atherosclerosis was found.

Major Acute Symptoms with AMI in Women

National Institute of Nursing Research
515 women diagnosed with acute MI

<table>
<thead>
<tr>
<th>Major Sx Preceding AMI</th>
<th>Major Sx During AMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unusual fatigue</td>
<td>SOB</td>
</tr>
<tr>
<td>Sleep disturbance</td>
<td>Weakness</td>
</tr>
<tr>
<td>SOB</td>
<td>Unusual fatigue</td>
</tr>
<tr>
<td>Indigestion</td>
<td>Cold sweat</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Dizziness</td>
</tr>
<tr>
<td>No report chest pain</td>
<td>No report chest pain</td>
</tr>
</tbody>
</table>

70% 58%
48% 55%
42% 43%
39% 39%
35% 35%
>70% 43%

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<td>No report chest pain</td>
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</tbody>
</table>

70% 58%
48% 55%
42% 43%
39% 39%
35% 35%
>70% 43%
### How Good are the NCEP III Guidelines for Making Therapeutic Recommendations?

<table>
<thead>
<tr>
<th>288 pts with prior MI</th>
<th>Mean age 50 yrs</th>
<th>Mean LDL 126 mg/dl</th>
<th>16% LDL &gt; 160 mg/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men ≤55 (75%)</td>
<td>Women ≤65 (25%)</td>
<td>Other risk factors</td>
<td></td>
</tr>
<tr>
<td>BMI &gt;25 kg/m² 82%</td>
<td>HTN 40%</td>
<td>Family Hx 42%</td>
<td></td>
</tr>
<tr>
<td>Cigarettes 60%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Akush JACC 2003;41:1475-9

### Premature MI & NCEP III Guidelines

- Those with 0-1 risk factors:
  - 50% of the 288 patients
  - Of these, 8% LDL >160
- Those with 2+ risk factors and <10% risk:
  - 2% met criteria for Rx
- Those with 2+ risk factors and 10-20% risk:
  - Only 45% met criteria for Rx
- Overall 74% would not have met criteria for drug therapy under NCEP III

Akush JACC 2003;41:1475-9

### Family History May be the Most Important Early Risk Factor of CHD

- Most early CV events occur in families with a positive history of CV disease
- 14% of general US population have a family history of premature CHD
- These families with a history of premature CHD account for 72% of new cases of premature CHD

Williams Am J Card;2001;87:129
Linton Am J Card 2003;92:191
Family History of Premature CHD Is Associated with Metabolic Syndrome

- There is a clustering of risk factors in patients with premature CHD and asymptomatic family members:
  - Hyperinsulinemia
  - Dyslipidemia
  - High fibrinogen
- Should a family history of metabolic syndrome be as a risk factor for CHD?


Risk Assessment Of Our 54 Year Old Lady With an MI

- Metabolic Syndrome
  - TG 200 +
  - HDL 42 +
  - BP 138/88 +
  - FBS 120 +
  - Waist 36” +
- She has 5/5 criteria

Grundy Circ 2004;109:369:433

Is Metabolic Syndrome a CHD Risk Equivalent?

- Metabolic Syndrome alone accounted for ~25% of CHD
- In absence of diabetes most patients with metabolic syndrome did not exceed the 20% 10 year risk for CHD, most were in the 10-20% risk group
- So how do we determine who is at high risk with metabolic syndrome?

Grundy Circ 2004;109:369:433
Metabolic Syndrome as a Predictor of CHD and Diabetes (WOSCOPS 5974 men)

Sattar Circ 2003;108:414

What is Important for CVD Risk Prediction?

Traditional risk factors
- Age, family history CHD, smoking

Traditional risk predictors
- Age, TC, HDL-C, Blood pressure, smoking

Risk equivalents
- Presence of DM, PVD

Emerging risk factors
- Metabolic Syndrome 5/5
- Family history of diabetes
- Family history of metabolic syndrome
- (CRP, PAI-1, small LDL, small HDL, remnant lipoproteins, apolipoprotein B, TG:HDL >4)

When asked, Is it better to love or be loved, the modern day philosopher Allen Konigsberg\(^1\) responded

“It really doesn’t matter if your cholesterol is high”

\(^1\) A.K.A. Woody Allen
Post Test Question
1. Which of the following statements is true?
   a. Fasting blood glucose better predicts diabetes than does metabolic syndrome
   b. Five parameters are included in the definition of metabolic syndrome. The presence of any 3 is sufficient to make the diagnosis.
   c. The risk for cardiovascular disease increases almost 3-fold for each additional component of metabolic syndrome
   d. The inclusion of abnormal levels of adiponectin and leptin have recently been included in the definition of metabolic syndrome

Post Test Question
2. Which of the following statements is true about metabolic syndrome
   a. Smoking is stronger risk factor for predicting cardiovascular disease than is metabolic syndrome
   b. The identification of metabolic syndrome improves clinical outcomes
   c. Metabolic syndrome alone accounts for 60% of coronary heart disease
   d. People with diabetes also have metabolic syndrome

Post Test Question
6. Which of the following statements is true?
   a. Waist circumference accurately predicts insulin resistance
   b. Family history may be the most important factor for predicting premature cardiovascular disease
   c. Insulin resistance is the basic defect causing cardiovascular disease
   d. People with diabetes also have metabolic syndrome