Improved Recognition of the Metabolic Syndrome: Other Clues to the Presence of Insulin Resistance

BRRH Grand Rounds

November 29, 2016

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The Only Known Picture of Lincoln Giving the Gettysburg Address
Why Do We Care About the Metabolic Syndrome (MBS)?

• A large segment of our patient population is affected by these associated conditions

• Compared to those without the syndrome, those with the syndrome have:
  • ~ 2-3-fold increase in relative risk for ASCVD events
  • ~ 5-fold increase in risk for developing diabetes

• Importantly, identification of these patients may occur before these complications occur, presenting clinicians with a unique opportunity to practice real evidence based, preventative medicine
NHANES III: Age-Specific Prevalence of the Metabolic Syndrome

Age-adjusted prevalence of the metabolic syndrome is 23.7%.
Approximately 47 million US residents have the metabolic syndrome.

Prevalence of the NCEP Metabolic Syndrome: NHANES III by Sex and Race/Ethnicity

- **White**
  - Men: 25%
  - Women: 23%

- **African American**
  - Men: 16%
  - Women: 26%

- **Mexican American**
  - Men: 28%
  - Women: 36%

- **Other**
  - Men: 21%
  - Women: 20%

Outline

I. History/Definition of the Metabolic Syndrome

II. Pathophysiology/Accuracy of the Current Definition in Identifying Insulin Resistance

III. Other Medical Conditions Associated with the Metabolic Syndrome

IV. Conclusions
History of the Metabolic Syndrome

- Frequent simultaneous presence of obesity, hyperlipidemia, diabetes, and HTN was first described in the late 1960s
- First called the Metabolic Syndrome in the late 1970s
- 1991: insulin resistance was recognized as a likely cause, and the name Insulin Resistance Syndrome was coined
- At about the same time, Reaven suggested the term Syndrome X
2001 NCEP ATP III Report

• Provided a definition for the Metabolic Syndrome (MBS) and identified it as a secondary target of risk-reduction therapy after the primary target, LDL-C

• The risk factors of the MBS are highly concordant, and in aggregate, they enhance the risk for CHD at any given level of LDL-C

• First line therapies for all lipid and non-lipid risk factors associated with the MBS are weight reduction and increased physical activity, which will effectively reduce all of these risk factors

(JAMA 2001; 285: 2486-2497)
### Various Definitions of the MBS

#### Table 1. Definitions of metabolic syndrome

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Absolutely required</td>
<td>None</td>
<td>Insulin resistance* (IGT, IFG, T2D or other evidence of IR)</td>
<td>Hyperinsulinemia^ (plasma insulin &gt;75^th percentile)</td>
<td>Central obesity (waist circumference^): ≥94 cm (M), ≥80 cm (F)</td>
</tr>
<tr>
<td>Criteria</td>
<td>Any three of the five criteria below</td>
<td>Insulin resistance or diabetes, plus two of the five criteria below</td>
<td>Hyperinsulinemia, plus two of the four criteria below</td>
<td>Obesity, plus two of the four criteria below</td>
</tr>
<tr>
<td>Obesity</td>
<td>Waist circumference: &gt;40 inches (M), &gt;35 inches (F)</td>
<td>Waist/hip ratio: &gt;0.90 (M), &gt;0.85 (F); or BMI &gt;30 kg/m²</td>
<td>Waist circumference: ≥94 cm (M), ≥80 cm (F)</td>
<td>Central obesity already required</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>Fasting glucose ≥100 mg/dl or Rx</td>
<td>Insulin resistance already required</td>
<td>Insulin resistance already required</td>
<td>Fasting glucose ≥100 mg/dl</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>TG ≥150 mg/dl or Rx</td>
<td>TG ≥150 mg/dl or HDL-C: &lt;35 mg/dl (M), &lt;39 mg/dl (F)</td>
<td>TG ≥177 mg/dl or HDL-C &lt;39 mg/dl</td>
<td>TG ≥150 mg/dl or Rx</td>
</tr>
<tr>
<td>Dyslipidemia (second, separate criteria)</td>
<td>HDL cholesterol: &lt;40 mg/dl (M), &lt;50 mg/dl (F); or Rx</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>&gt;130 mmHg systolic or &gt;85 mmHg diastolic or Rx</td>
<td>≥140/90 mmHg</td>
<td>≥140/90 mmHg or Rx</td>
<td>&gt;130 mmHg systolic or &gt;85 mmHg diastolic or Rx</td>
</tr>
</tbody>
</table>

*IGT, impaired glucose tolerance; IFG, impaired fasting glucose; T2D, type 2 diabetes; IR, insulin resistance; other evidence includes euglycemic clamp studies.
^Urinary albumin excretion of ≥20 µg/min or albumin-to-creatinine ratio of ≥30 mg/g.
Reliable only in patients without T2D.
^Criteria for central obesity (waist circumference) are specific for each population; values given are for European men and women.
Rx, pharmacologic treatment.

- Identified 6 components of the MBS that relate to CVD:
  1. Abdominal obesity
  2. Atherogenic dyslipidemia
  3. Raised blood pressure
  4. Insulin resistance ± glucose intolerance
  5. Proinflammatory state
  6. Prothrombotic state

(Circulation 2004; 109: 433-438)
• Atherogenic dyslipidemia includes increased levels of remnant lipoproteins (especially large VLDL particles), Apolipoprotein B, and small LDL and HDL particles

• A proinflammatory state is recognized clinically by elevations of CRP levels

• A prothrombotic state is characterized by increased levels of plasminogen activator inhibitor-1 (PAI-1) and fibrinogen
# 2005 Revised Diagnostic Criteria for the Metabolic Syndrome

TABLE 4. The American Heart Association and National Heart, Lung, and Blood Institute Updated ATP III Classification: 2005*

<table>
<thead>
<tr>
<th>Any 3 of 5 criteria listed below constitute a diagnosis of metabolic syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Categorical cut points:</strong></td>
</tr>
<tr>
<td>Elevated waist circumference†: 102 cm in men and 88 cm in women</td>
</tr>
<tr>
<td>Elevated TG: 150 mg/dL (1.7 mmol/L) or drug treatment for elevated TG‡</td>
</tr>
<tr>
<td>Reduced HDL-C: 40 mg/dL (0.9 mmol/L) in men, 50 mg/dL (1.1 mmol/L) in women, or drug treatment for reduced HDL-C‡</td>
</tr>
<tr>
<td>Elevated BP: 130 mm Hg systolic BP or 85 mm Hg diastolic BP, or drug treatment for hypertension</td>
</tr>
<tr>
<td>Elevated fasting glucose: 100 mg/dL or drug treatment for elevated glucose</td>
</tr>
</tbody>
</table>

*TG indicates triglycerides; BP, blood pressure.

†Some US adults of non-Asian origin (eg, white, black, Hispanic) with marginally increased waist circumference (eg, 94–102 cm [37–39 inches] in men and 80–88 cm [31–35 inches] in women) may have strong genetic contribution to insulin resistance and should benefit from changes in lifestyle habits, similar to men with categorical increases in waist circumference. Lower waist circumference cut point (eg, 90 cm [35 inches] in men and 80 cm [31 inches] in women) appears to be appropriate for Asian Americans.

‡Fibrates and nicotinic acid are the most commonly used drugs for elevated TG and reduced HDL-C. Patients taking 1 of these drugs are presumed to have high TG and low HDL.

(Circulation 2005; 112: e285-e290)
<table>
<thead>
<tr>
<th>Country/Ethnic group</th>
<th>Waist circumference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europids*</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>≥ 94 cm</td>
</tr>
<tr>
<td>Female</td>
<td>≥ 80 cm</td>
</tr>
<tr>
<td>In the USA, the ATP III values (102 cm male; 88 cm female) are likely to continue to be used for clinical purposes</td>
<td></td>
</tr>
<tr>
<td>South Asians</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>≥ 90 cm</td>
</tr>
<tr>
<td>Female</td>
<td>≥ 80 cm</td>
</tr>
<tr>
<td>Based on a Chinese, Malay and Asian-Indian population</td>
<td></td>
</tr>
<tr>
<td>Chinese</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>≥ 90 cm</td>
</tr>
<tr>
<td>Female</td>
<td>≥ 80 cm</td>
</tr>
<tr>
<td>Japanese**</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>≥ 90 cm</td>
</tr>
<tr>
<td>Female</td>
<td>≥ 80 cm</td>
</tr>
<tr>
<td>Ethnic South and Central Americans</td>
<td>Use South Asian recommendations until more specific data are available</td>
</tr>
<tr>
<td>Sub-Saharan Africans</td>
<td>Use European data until more specific data are available</td>
</tr>
<tr>
<td>Eastern Mediterranean and Middle East (Arab) populations</td>
<td>Use European data until more specific data are available</td>
</tr>
</tbody>
</table>

* In future epidemiological studies of populations of Europid origin, prevalence should be given using both European and North American cut-points to allow better comparisons.

** Originally different values were proposed for Japanese people but new data support the use of the values shown above.
Differences in the Prevalence (%) of Metabolic Syndrome between Asian Indians and Whites by Body Mass Index

<table>
<thead>
<tr>
<th>BMI</th>
<th>Whites</th>
<th>Asian Indians</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;25</td>
<td>10%</td>
<td>38%</td>
</tr>
<tr>
<td>25-29.9</td>
<td>25%</td>
<td>50%</td>
</tr>
<tr>
<td>30-34.9</td>
<td>45%</td>
<td>65%</td>
</tr>
<tr>
<td>&gt;35</td>
<td>58%</td>
<td>80%</td>
</tr>
</tbody>
</table>
Main Pathophysiological Defects in T2DM

The Ominous Octet

- Islet β-cell
  - Impaired Insulin Secretion
  - Decreased Incretin Effect
  - Increased Lipolysis
  - Increased Glucagon Secretion
  - Increased HGP
  - Neurotransmitter Dysfunction

- Islet α-cell

Hyperglycemia

Increased Glucose Reabsorption

Decreased Glucose Uptake

( Diabetes 2009; 58: 773-795)
Lipid and Lipoprotein Abnormalities Associated with Insulin Resistance and Type 2 DM

Onset of Lipoprotein Abnormalities

Peripheral Insulin Resistance

Plasma Insulin

PP Glucose

Fasting Glucose

Time

Macrovascular Disease

Type II DM

Microvascular Disease
Insulin Resistance (IR) and Glucose Intolerance

- Patients with longstanding insulin resistance (IR) frequently manifest glucose intolerance.
- Impaired Fasting Glucose (IFG) is currently recognized as a fasting glucose $\geq 100$ mg/dl.
- Post-glucose challenge glucose levels provide a more sensitive indicator of IR.
- An alternative is Hgb-A1c: 5.7 – 6.4% = pre-diabetes and $\geq 6.5$% = diabetes.
Measuring Insulin Resistance (IR)

- IR generally rises with increasing body fat content; however, a broad range of insulin sensitivities exists at any given level of body fat.

- In other words, although being overweight/obese is associated with an increased risk of being insulin resistant, not all overweight/obese people are insulin resistant, and not all insulin resistant people are overweight/obese!

- Since patients with IR are high risk, how do we best identify them?
Measuring Insulin Resistance (IR)

- Direct measures of insulin-mediated glucose disposal are not clinically practical
- Both fasting and post-glucose challenge plasma insulin concentrations are useful surrogate markers of IR
- However:
  1. Assays for plasma insulin are not standardized
  2. There are not reliable data to define an individual as being insulin resistant on the basis of an insulin concentrations alone
  3. It has also not been established that an increased plasma insulin level in the absence of other criteria can predict the development of CVD
Use of Metabolic Markers to Identify Overweight Individuals Who are Insulin Resistant *(Ann Intern Med 2003; 139: 802 – 809)*

- 258 nondiabetic, normotensive overweight volunteers (BMI = 25 – 39.1 kg/m2)
- All underwent a modified insulin suppression test (highly correlated with the “gold standard” euglycemic, hyperinsulinemic clamp test)
- IR was defined as being in the upper tertile of steady-state plasma glucose
- Metabolic markers, including the ATP III definition of the MBS, were measured to determine which best identified patients in this upper tertile of IR
Use of Metabolic Markers to Identify Overweight Individuals Who are Insulin Resistant (cont.)

- 50% of the subjects fell into the most insulin resistant (upper) tertile

- The best markers were: a) TG/HDL-C ≥ 3, b) TGs ≥ 130 mg/dl, and c) a fasting Insulin ≥ 108 pmol/L

- Meeting the ATP III Criteria for the MBS had a sensitivity of only 52% in identifying the most insulin resistant subjects
Interpretation of Test Results

- IR and many other traits of the MBS are continuous variables, with no absolute cut-off between normal and abnormal.
- Those fitting the definition of the syndrome are likely to be the most insulin resistant, and the easiest to identify.
- Many patients with lesser degrees of insulin resistance (sometimes with “normal” test results) are thus missed, and a crucial opportunity lost!!!
Other Conditions Associated with IR

1. Family history of T2DM/CAD
2. Overactive Sympathetic NS
3. Elevated uric acid levels/Gout
4. Fatty Liver
5. PCOS
6. OSA
7. Gestational DM
8. Hypertriglyceridemia due to Accutane
9. HIV/AIDS
Other Conditions Associated with IR

10. Low levels of Testosterone

11. CKD

12. Stress-induced Hyperglycemia

13. Elevated levels of small dense LDL-P, large VLDL-P, and reduced levels of large HDL-P
Family History of T2DM and CAD

- 1º relatives of patients with T2DM have an approximately 3-fold greater lifetime risk of developing T2DM than the general population.

- Atherogenic Dyslipidemia (↑ TGs, ↓ HDL-C, and ↑ small, dense LDL-P) is found in 50% of male CAD patients, and is a potent risk factor for the development of T2DM.

- The Bogalusa Heart Study showed that central obesity and fasting insulin levels were consistently higher in the offspring of those with CAD.
Overactivity of the Sympathetic Nervous System (SNS)

- Stimulation and overactivity of the SNS are known to be involved in the pathogenesis of HTN
- Evidence of autonomic dysfunction is commonly seen in obesity, IR, and T2DM
- Clinical indicators include elevated resting HR (> 75 bpm), reduced HR variability, delayed HR recovery after exercise, a hypertensive response to exercise, and increased arterial stiffness
Hyperuricemia/Gout

- Uric acid concentrations are higher in individuals with IR, due to reduced clearance of uric acid by the kidneys.

- Whether uric acid is an independent risk factor for CVD is controversial, but its link to IR may explain some or all of this relationship.

- Xanthine oxidase, the enzyme responsible for the formation of uric acid, is a major producer of reactive oxygen species in the endothelium—this may provide a link between uric acid levels, endothelial dysfunction, and markers of inflammation.
Hyperuricemia/Gout

- A fructose-rich diet can raise uric acid production.
- Uric acid levels are an independent risk factor for the development of HTN, as well as for a non-dipper circadian pattern of HTN.
- Levels ≥ 5.5 mg/dl indicate an increased likelihood of pre-eclampsia in hypertensive pregnant patients.
- A meta-analysis of 11 studies revealed a 17% increased risk of DM for every mg/dl increase in uric acid.
Non-alcoholic Fatty Liver Disease (NAFLD)

- Estimated to affect approximately 1/3 of the western population, making it the most common cause of altered LFTs, and one of the most common causes of end-stage liver disease requiring transplantation
- Represents a spectrum of disease
- Can also occur in lean subjects (BMI < 25)
- Increased lipolysis results in an increased flux of free fatty acids to the liver, which causes increased production of VLDL and fat deposition
Non-alcoholic Fatty Liver Disease (NAFLD)

- Traditionally regarded as the hepatic manifestation of the MBS
- However, there is debate about the “chicken or egg”, and the relationship is bidirectional
Stress-Induced Hyperglycemia

- Concept is the same as developing hyperglycemia or diabetes during “physiologic stress”, like pregnancy.
- Very commonly seen among hospital inpatients, but best described in those with ACS
- Also commonly seen in ICU and post-surgical patients, as well as those with any significant acute illness
- Often represents an unmasking of a latent tendency, and more common among those with other risk factors (i.e. overweight, family history of DM, etc....)
Lipoprotein Abnormalities

- The presence of increased levels of large VLDL, small LDL, and small HDL particles reflect and predict the presence of IR

- Elevated levels of Apo B-containing lipoproteins (all of which are atherogenic) are also present

- There are varying degrees of discordance between LDL-C and Apo B/LDL particle number depending on the severity of the underlying IR (often leading to under treatment)
Lipoprotein Abnormalities in Insulin Resistance

1. Hepatic Synthetic Abnormalities
   - ↑ TG Synthesis
   - ↑ Gluconeogenesis
   - ↓ Apo B Degradation
   - ↑ VLDL Synthesis

2. VLDL Production Abnormalities
   - ↑ Number Large VLDL particles

3. VLDL Clearance Abnormalities
   - ↓ LPL Enzyme Activity
   - ↑ Number VLDL particles

4. CETP Abnormalities
   - ↑ Enzyme Mass
   - ↑ Enzyme Activity

5. LDL Abnormalities
   - ↑ Total Number particles
   - ↑ Number Small particles

6. HDL Abnormalities
   - ↓ Number Large Particles
   - ↑ Number Small Particles

Liver

- ↑ Peripheral Tissue Insulin Resistance
- ↑ NEFA Delivery
Hypertriglyceridermia due to treatment with Isotretinoin (Accutane)

- Isotretinoin (13-cis retinoic acid) is a treatment for severe acne resistant to other treatments
- About 20% of patients treated with this drug will develop a marked, but reversible elevation in plasma concentrations of TGs (TG-rich lipoproteins), which can result in acute pancreatitis
- Those patients with this response are significantly more likely to develop manifestations of the MBS in the future
- Treatment with the drug is a “metabolic stress test”

Polycystic Ovary Syndrome (PCOS)

- The most common endocrine disorder seen in women of reproductive age, and characterized by oligo- /amenorrhea, clinical or biochemical signs of hyperandrogenism, and polycystic ovaries (variable)

- More than 40% of PCOS patients are obese with central fat distribution, and at least 50-70% show evidence of hyperinsulinemia/IR

- 40-50% meet criteria for the MBS, up to 30% have IGT, and an additional 7.5% have diabetes
Polycystic Ovary Syndrome (PCOS)

- Commonly have elevated TGs (increased VLDL particles), low HDL-C, and increased small, dense LDL
- Also have evidence of elevated levels of oxidative stress and inflammation
- Significantly increased risk to develop diabetes and ASCVD
- Both Metformin and Thiazolidinediones are useful in treatment
Obstructive Sleep Apnea (OSA)

- Sleep deprivation is known to cause diminished insulin sensitivity
- “Syndrome Z” has been proposed as the name for the combination of the MBS (Syndrome X) and OSA, to reflect the close association of the two conditions
- Sleep apnea is also significantly more common in women who have PCOS (central obesity, insulin resistance, and hyperinsulinemia)
- Again, a bidirectional relationship is seen between OSA and the MBS
Obstructive Sleep Apnea (OSA)

- OSA is one of the major causes of resistant HTN, and treatment with CPAP has a more significant BP-lowering effect in these patients.

- OSA is also associated with an increased risk of CHF, arrhythmias (atrial fibrillation), and stroke.

- Multiple mechanisms link the 2 conditions, including IR, Sympathetic Nervous System overactivity, hormonal changes, systemic inflammation, oxidative stress, and endothelial dysfunction.
Gestational Diabetes (GDM)

- Pregnancy induces a milieu characterized by insulin resistance, thus producing a “metabolic stress test”
- Women with a past history of GDM have at least a 3-fold higher prevalence of the MBS after pregnancy
- Women with MBS in early pregnancy have a greater risk of developing GDM
- GDM shares several common risk factors with T2DM and the MBS: family history of diabetes, increased age, and overweight/obesity
Gestational Diabetes (GDM)

- Women with the MBS are at increased risk of developing pre-eclampsia, and women with elevated BP during pregnancy have an increased risk of CVD later in life.
- Women with GDM have an elevated risk of CVD, even in the absence of T2DM.
- Low birthweight babies have an increased risk for the development of HTN, T2DM, and CVD later in life.
- On the other hand, large gestational-age babies and babies of obese mothers also have an increased risk for developing the MBS.
Low Levels of Testosterone (T)

- 30-40% of men with T2DM may have low T levels, characteristically with low gonadotrophin concentrations
- There is a strong inverse relation between total/free T with insulin levels and visceral fat accumulation
- Convincing evidence that low T is an independent RF for development of the MBS
- Again, there is a bidirectional relationship, as MBS can cause low T levels
Hypogonadal-Obesity-Adipocytokine Hypothesis

(Ther Adv Endocrinol Metab 2010; 1: 209)
Low Levels of Testosterone (T)

- Male patients with prostate cancer treated with androgen deprivation therapy (ADT) have been shown to have an increased risk of developing T2DM and CVD compared to untreated patients or those treated with other modalities.

- Men with Klinefelter’s Syndrome (XXY), the most common classical form of hypogonadism, have an increased risk of death from T2DM and CVD.
HIV +/AIDS Patients

- Among HIV-infected individuals, the introduction and widespread use of HAART in the mid-1990s lead to a dramatic decline in immunodeficiency-related illness, including death.

- Consequently, life expectancy and the burden of chronic illnesses has increased in this population.

- Reported prevalence of the MBS in the HIV population range from 11.2 – 45.4%.
HIV +/AIDS Patients

• The natural course of HIV infection is associated with lipid abnormalities (↓ HDL-C, ↑ TGs/VLDL, ↑ sd LDL), lipodystrophy, insulin resistance, and a deregulated inflammatory response.

• HAART causes these same metabolic complications to a greater extent (Protease Inhibitors are the most widely recognized).

• Longitudinal follow up of the DAD Cohort showed a 26% increase in the rate of MI/year of exposure to HAART during the first 4-6 years of treatment.
HIV +/AIDS Patients

- Obesity/overweight are more prevalent in the HIV population than wasting
- Smoking is very prevalent in the HIV population
- There is evidence showing that HIV patients who maintained virologic suppression on effective HAART obtained additional survival benefit from the use of a statin
Chronic Kidney Disease (CKD)

- Microalbuminuria, a common manifestation of the MBS, is a predictor of progressive kidney disease.

- Obesity/↑ central fat are independently associated with renal dysfunction (i.e. focal segmental glomerulosclerosis and glomerulomegaly).

- ↓ HDL-C and ↑ TGs are independently associated with an increased risk for CKD, and are the most common lipid abnormalities seen in patients with CKD.

- NHANES III: a 2.6 fold increase in the prevalence of CKD among adults with the MBS.
Conclusions

1. MBS affects a large segment of the adult population, especially the elderly and certain ethnic groups.

2. In addition to the usual components, MBS includes microalbuminuria, and both pro-inflammatory and pro-thrombotic states.

3. Insulin resistance, and the resulting compensatory hyperinsulinemia, are the main pathophysiologic abnormalities causing the MBS.

4. A fasting insulin level, a surrogate marker of IR, can be measured, but is not necessary to make the diagnosis.
Conclusions

5. MBS is associated with a large number of other medical conditions, across a wide range of medical specialties.

6. Recognition of these additional associations should prompt clinicians to more aggressively look for and diagnose the MBS.

7. Improved/earlier diagnosis of the MBS provides clinicians with a major opportunity to practice true preventative and evidence-based medicine, which focuses on therapeutic lifestyle change.