Metabolic Syndrome: An overview.

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Setting the scene

- GB, 43 yo AA man followed for hypothyroidism returns on LT4 125 mcg/d and has a TSH=1.1 mU/l (normal)
- Weight: 208 lbs (↑from 189 over 1.5 yrs)
- Height: 5’10” (BMI=29) (Overweight; Obese>30)
- Waist circumference: 42” (>40 high risk)
- BP 130/85 mmHg (borderline; HBP 140/90)
- Tg = 178 mg/dl (high <150), HDL = 36 mg/dl (low>40), LDL =129 mg/dl (high <100), fasting glucose= 112 mg/dl (prediabetes; >126 diabetes)
The response

• Physician: “You need to lose weight”

• Patient: “?”
Cardiovascular risk: Framingham

- Sex
- Blood pressure
- Cholesterol
- Smoking
- Diabetes
Cardiovascular risk: Framingham

1960

1961: Sex

1961: Blood pressure

1961: Cholesterol

1974: Smoking

1974: Diabetes

1991: Risk prediction model

http://www.nhlbi.nih.gov/about/framingham/timeline.htm
Addressing "classical risk": risk factors

Heart Protection Study, Lancet 2002
The evolving landscape
Cardiovascular disease: the landscape since Framingham 1985-2005

Mokdad et al., BRFSS CDC
Cardiovascular burden of obesity

The new landscape

Source: NCHS and CDC
Why is obesity bad?
The endocrine adipocyte.

- Resistin
- Adiponectin
- Estrogen
- Ang II
- Angiotensinogen
- Leptin
- PAI-1
- Bone Morphogenic Protein
- IGF-1 IGFBP
- TNF-α Interleukins TGF β FGF EGF
- Fatty Acids Lactate Adenosine Prostaglandins Glutamine
- Unknown Factors

Good fat – bad fat??

Abdominal (Android)

Lower Body (Gynoid)
Metabolic Syndrome

- Triglyceride
  - Intramuscular droplet
- Hypertension
- FFA
- Adiponectin
- PAI-1
- Fibrinogen
- C-reactive protein
- HDL cholesterol
- Small dense LDL
- TNFα
- Interleukin 6
- Prothrombic state
- Glycogen
- CO2
- Triglyceride (intramuscular droplet)

Eckel Lancet 2005
“Metabolic syndrome” Conceptualization

• An insulin resistance disorder
• An inflammatory disorder
• A prothrombotic disorder
• A controversial disorder

Resulting in increased cardiometabolic risk
Metabolic Syndrome: ATP III

3 or more of the following:

- Central obesity as measured by waist circumference:
  Men — Greater than or equal to 40 inches
  Women — Greater than or equal to 35 inches
- Fasting blood triglycerides greater than or equal to 150 mg/dL
- Blood HDL cholesterol:
  Men — Less than 40 mg/dL
  Women — Less than 50 mg/dL
- Blood pressure greater than or equal to 130/85 mmHg
- Fasting glucose greater than or equal to 100 mg/dL
What is Cardiometabolic Risk?
Beyond Framingham

- Type 2 Diabetes
- Elevated Blood Pressure
- Elevated LDL
- Smoking
- Inflammatory Markers
- Elevated Triglycerides
- Elevated Blood Glucose
- Abdominal Adiposity
- Insulin Resistance
- Low HDL
- CVD
Does metabolic syndrome increase morbidity or mortality?

![Graph showing prevalence and mortality of different conditions with and without metabolic syndrome.](WHO criteria, Botnia cohort, Isomaa, Diabetes Care 2001)
Obesity correlates with (and we are learning, causes):

- Insulin resistance
- Hypertension
- Dyslipidemia
- Diabetes
- Inflammation
- Impaired fibrinolysis
Increased adiposity yields insulin resistance and risk of diabetes (dramatically)

Visceral adiposity is correlated with peripheral insulin resistance


![Graph showing correlation between visceral adipose tissue volume and insulin-mediated glucose disposal](image-url)
Inherent risk: diabetes dyslipidemia

7-Year Incidence of Fatal/Nonfatal MI

- Nondiabetic
- Diabetic

<table>
<thead>
<tr>
<th>Incidence (%)</th>
<th>Nondiabetic</th>
<th>Diabetic</th>
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<tbody>
<tr>
<td>No DM, No MI</td>
<td>3.5</td>
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<td>N = 1304</td>
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<td>No DM, MI</td>
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<td>N = 69</td>
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<tr>
<td>DM, No MI</td>
<td></td>
<td>45.0</td>
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<td>N = 890</td>
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<td></td>
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<tr>
<td>DM, MI</td>
<td></td>
<td></td>
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<tr>
<td>N = 169</td>
<td></td>
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</tr>
</tbody>
</table>

WOW!

Obesity and Cardiometabolic risk

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Obesity dyslipidemia

- Triglyceride
- Hypertension
- FFA
- PAI-1
- Fibrinogen
- Prothrombic state
- Adiponectin
- Glucose
- TNFα
- Interleukin 6
- Insulin
- Sympathetic nervous system
- HDL cholesterol
- Small dense LDL
- Insulin
- Glycogen
- CO2
- VLDL
- C-reactive protein
- C-II
- C-III
- B-100 and

Eckel Lancet 2005
Obesity dyslipidemia

Hypercholesterolemia

Hypertriglyceridemia

Low and “abnormal” HDL cholesterol

“Abnormal” LDL cholesterol
Insulin resistance and hypertriglyceridemia

* Total area under 3-hour response curve (mean of 2 tests).
Obesity dyslipidemia

Insulin → FFA → Liver

TTG

ApoB
Plasma insulin, triglycerides and ischemic heart disease
Quebec Cardiovascular Study


**Fasting-Insulin (µU/ml)**

- **<12**
  - Odds Ratio: 1.0
  - P-value: 0.005

- **12-15**
  - Odds Ratio: 4.6
  - P-value: 0.002

- **>15**
  - Odds Ratio: 5.4
  - P-value: 0.001

**Triglycerides**

- **<150 mg/dl**
  - Odds Ratio: 5.3
  - P-value: 0.001

- **>150 mg/dl**
  - Odds Ratio: 6.7
  - P-value: <0.001
Obesity dyslipidemia

Fat Cells → Liver

- ↑ FFA
- ↑ TG
- ↑ ApoB
- ↑ VLDL

Liver → Kidney

- CETP
- CE
- TG
- HDL
- LDL
- VLDL
- SD LDL

Insulin

IR

Kidney

Apo A-1

Lipids online (Ginsberg)
Is hepatic VLDL production a therapeutic target?

- Increasingly triglycerides are recognized as a cardiovascular risk factor
  - VA-HIT, Helsinki Heart, Physicians Health study, EPIC-Norfolk
  - Diabetics: WHO MSVDD
  - Elderly, known CAD: CARE
43 yo AA man followed for hypothyroidism returns on LT4 125 mcg/d and has a TSH=1.1 mU/l (normal)

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Obesity, hypertension, and fibrinolysis

Muniyappa, Endocr. Rev. 28(5): 463
Endothelial function

- Vasodilation
- Anti-atherogenic
- Thrombolysis
- Other effects?

eNOS and hypertension

• Pharmacological inhibition of eNOS (n=7):

  $109(5)/65(3) \xrightarrow{} 133(9)/79(5)$

• Carotid wall “stiffness”

  $9.8(1.2) \xrightarrow{} 12.6(2.0)$

Sugawara et al., Hypertension Res. 30(5) 2007
Obesity and cardiometabolic risk

- GB, 43 yo AA man followed for hypothyroidism returns on LT4 125 mcg/d and has a TSH=1.1 mU/l.
- Weight has increased from 189-208 over the last 18 months. He is 5’10” (BMI=29); waist circumference is 42”; BP=130/85
- Fasting lipids: Tg = 178 mg/dl, HDL = 36 mg/dl, LDL = 129 mg/dl, fasting glucose= 112 mg/dl
PAI-1 increases with BMI

Skurk, Int. J. of Obesity 2004
# Insulin resistance as the defining lesion of metabolic syndrome

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Insulin effect</th>
<th>Resistance</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>Reduce food intake</td>
<td>Increased food intake</td>
<td>NPY/POMC</td>
</tr>
<tr>
<td>Liver</td>
<td>Suppress HGP</td>
<td>Hyperglycemia</td>
<td>Glycogenolysis/GNG</td>
</tr>
<tr>
<td>Fat</td>
<td>Inhibit lipolysis/TG</td>
<td>lipolysis/inc FFA</td>
<td>HSL</td>
</tr>
<tr>
<td>Endothelium</td>
<td>Vasodilation</td>
<td>“dysfunction”/hypertension</td>
<td>PI3K-eNOS</td>
</tr>
</tbody>
</table>
Why insulin (and glucose)?

Norhammer et al., (Lancet 2002) prospectively studied 181 acute MIs with no prior diagnosis of diabetes:

- 31% IGT
- 35% diabetes
Conclusions

• Obesity is associated with:
  – Insulin resistance
  – Inflammation
  – Impaired fibrinolysis
• And:
  – Hypertension
  – Dyslipidemia
  – Diabetes
  – Cardiovascular disease
• Mechanisms involved are increasingly coming to light