Metabolic Syndrome: An overview.

Kevin Niswender MD, PhD
Vanderbilt University School of Medicine
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.

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
The response

• Physician: “You need to lose weight”

• Patient: “You look overweight yourself. Why do I need to lose weight?”
Cardiovascular risk: Framingham

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

- Sex
- Cholesterol
- Diabetes
- Smoking
- Blood pressure

1960: Addition of cholesterol
1961: Addition of smoking
1974: Addition of diabetes
1991: Risk prediction model

http://www.nhlbi.nih.gov/about/framingham/timeline.htm
Addressing “classic” risk: risk factors

Heart Protection Study, Lancet 2002

20-25% risk reduction

Persistent risk

Benefit/1000 (SE): 5(3) 20(4) 35(5) 46(5) 54(7) 60(18)

Unaddressed risk: statins

LDL (mg/dl)

Statin        placebo

131
89
131
127

50 75 100 125 150

Benefit/1000 (SE): 5(3) 20(4) 35(5) 46(5) 54(7) 60(18)
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
- IGF-1 IGFBP
- Bone Morphogenic Protein
- PAI-1
- 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

Hypertension

Interleukin 6
Insulin
Sympathetic nervous system

FFA

Insulin

Glucose

TNFα
Interleukin 6

Adiponectin

C-reactive protein

Triglyceride
VLDL

Fibrinogen

PAI-1

Prothrombic state

C-II
C-III
B-100 and

Triglyceride

HDL cholesterol
Small dense LDL

↓

Small dense LDL

 ↓

C-reactive protein

Glycogen

CO₂

Interleukin 6

Eckel Lancet 2005

Kevin Niswender 2009
“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
- Smoking
- Elevated LDL
- Elevated Blood Glucose
- Inflammatory Markers

CVD
- Elevated Triglycerides
- Abdominal Adiposity
- Insulin Resistance
- Low HDL

- Insulin Resistance
- Low HDL
Does metabolic syndrome increase morbidity or mortality?

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


p<0.005
Inherent risk: diabetes dyslipidemia

7-Year Incidence of Fatal/Nonfatal MI

- **Nondiabetic**
  - No DM, No MI: 3.5% (n = 1304)
  - No DM, MI: 18.8% (n = 69)

- **Diabetic**
  - DM, No MI: 20.2% (n = 890)
  - DM, MI: 45.0% (n = 169)

**P < 0.001**

WOW!

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
Obesity dyslipidemia

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

Liver

FFA

TG

ApoB
Plasma insulin, triglycerides and ischemic heart disease

Quebec Cardiovascular Study

Obesity dyslipidemia

Fat Cells ➔ FFA

Fat Cells ➔ Fat Cells ➔ Liver

Liver ➔ TG, ApoB, VLDL

Liver ➔ (CETP) ➔ LDL

Liver ➔ (CETP) ➔ CE

Liver ➔ HDL

Kidney ➔ Apo A-1

IR ➔ X

Insulin

Fat Cells ➔ ↑TG, ↑ApoB, ↑VLDL

Liver ➔ ↑VLDL

Liver ➔ (CETP) ➔ CE, TG

Liver ➔ (lipoprotein or hepatic lipase) ➔ SD LDL

Liver ➔ HDL

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
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
Obesity, hypertension, and fibrinolysis

Endothelial function

Vasodilation
Anti-atherogenic
Thrombolysis
Other effects?

eNOS and hypertension

• Pharmacological inhibition of eNOS (n=7):

  109(5)/65(3) $\rightarrow$ 133(9)/79(5)

• Carotid wall “stiffness”

  9.8(1.2) $\rightarrow$ 12.6(2.0)

Sugawara et al., Hypertension Res. 30(5) 2007
Endothelial dysfunction

- Vasoconstriction
- Smooth muscle proliferation
- Pro-atherotic

Hyperglycemia
Free fatty acids

Angiotensin II
Insulin

PI3K pathway
Selective insulin resistance

MAPK pathway

Endothelial cell

- NOX → PKC
- O₂⁻ → ONOO⁻
- eNOS uncoupling
- BH₂

Endothelial dysfunction

Thromboxane

Vascular smooth muscle cell

- PGIS → Prostacyclin synthase
- Nitrosylation

ET-1

ET-1 → Angiotensin II

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
Coagulation and Fibrinolysis

Coagulation Factors
- Fibrinogen
- Fibrin

Fibrinolysis
- t-PA, Urokinase
- Plasminogen
- Plasmin
- Lp(a)
- Homocysteine
- Cysteine
- Glutathione
- PAI-1

Lipids Online (Wilson)
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></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fat</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endothelium</td>
<td></td>
<td></td>
<td></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