THE METABOLIC SYNDROME: Pre-Diabetes, Hypertension and Heart Disease

Patrick Hanaway, MD
George Rodgers, MD
Clinical Questions will be answered during the final fifteen (15) minutes of the webinar.
Obesity Trends* Among U.S. Adults


(*BMI ≥30, or about 30 lbs. overweight for 5’4” person)
**Obesity Trends* Among U.S. Adults**

**BRFSS, 1990**

(*BMI ≥30, or ~30 lbs. overweight for 5’ 4” person)
**Obesity Trends* Among U.S. Adults**

*BRFSS, 1999*

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
**Obesity Trends* Among U.S. Adults**

*BRFSS, 2009*

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)*

![Map showing obesity trends among U.S. adults](image-url)
Overweight and Obesity Increasing
Most US Adults Weigh Too Much

• 66% of US adults are overweight or obese
  – 1 in 6 children are overweight

• Overweight
  – High weight for height

• Obese
  – Condition characterized by excess body fat
NHANES: Age-Specific Prevalence of the Metabolic Syndrome*

Age-adjusted prevalence of the metabolic syndrome is 34.6%

NHANES 1999-2002, N = 3,601
*NCEP ATP III definition of the metabolic syndrome

NHANES: Age-Adjusted Prevalence of the Metabolic Syndrome by Gender and Race*

NHANES 1999-2002, N = 3,601
*NCEP ATP III definition of the metabolic syndrome

Obesity Epidemic Drivers

- Abundance of fast foods
- Super sized portions
- Abundance of processed foods
- Lack of time to prepare meals
- Lack of time to exercise
- Economic challenges: two jobs
- Learned and reinforced behaviors
Health Impact of Obesity

- Type 2 Diabetes
- Metabolic Syndrome
- Hypertension
- Dyslipidemia
- Atherosclerosis
- PCOS
- Female masculinization
- Male feminization
- Hyperuricemia
- Liver disease: Fatty Liver, NASH
- Sleep Apnea
- Orthopedic issues: spine and joint
- Cancer: Breast, Billiary Cancer
Factors Contributing to Cardiometabolic Risk

Cardiometabolic Risk
Global Diabetes/CVD Risk

- Genetics
- Age
- Insulin Resistance
  - ↑Lipids
  - ↑BP
  - ↑Glucose

- Overweight/Obesity

- Abnormal Lipid Metabolism
  - LDL ↑
  - ApoB ↑
  - HDL ↓
  - Triglycerides ↑

- Smoking, Physical Inactivity
- Hypertension
- Inflammation, Hypercoagulation
- Age, Race, Gender, Family History

Genova Diagnostics
Innovative Testing for Optimal Health
The Obese Without Cardiometabolic Risk Factor Clustering and the Normal Weight With Cardiometabolic Risk Factor Clustering


Rachel P. Wildman, PhD; Paul Muntner, PhD; Kristi Reynolds, PhD; Aileen P. McGinn, PhD; Swapnil Rajpathak, MD, DrPH; Judith Wylie-Rosett, EdD; MaryFran R. Sowers, PhD

Rates of CardioMetabolic Syndrome

<table>
<thead>
<tr>
<th></th>
<th>BMI &lt; 25</th>
<th>BMI 25-30</th>
<th>BMI &gt;30</th>
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<tbody>
<tr>
<td>MEN</td>
<td>30%</td>
<td>51%</td>
<td>71%</td>
</tr>
<tr>
<td>WOMEN</td>
<td>21%</td>
<td>43%</td>
<td>65%</td>
</tr>
<tr>
<td>TOTAL</td>
<td>26%</td>
<td>46%</td>
<td>68%</td>
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</tbody>
</table>
A New Vital Sign: Waist Circumference

Abdominal adiposity

Hypertension

Dyslipidemia

Dysglycemia

Coronary Heart Disease

More about fat than you ever wanted to know . . . Adiposopathy!
More about fat than you ever wanted to know . . . Adiposopathy!
More about fat than you ever wanted to know . . . Adiposopathy!

More about fat than you ever wanted to know . . . Adiposopathy!

Indirect pathogenic effects of adiposopathy via onset or worsening of atherosclerotic coronary heart disease risk factors (e.g., diabetes mellitus, high blood pressure, dyslipidemia, metabolic syndrome, etc.)

Direct pathogenic effects of adiposopathy through promotion of atherosclerosis, endothelial dysfunction, and other vasculopathies via pericardial and perivascular adipose tissue dysfunction

Excess Abdominal Adiposity = High-Risk Fat

- Associated with inflammatory markers (C-reactive protein)
- Adiponectin (insulin sensitizer)
- Free fatty acids (FFAs)

Adipose Tissue as an Endocrine Organ

Traditional View
Fat is an inert storage depot

Emerging View
Fat is a secretory/endocrine organ

- Leptin, fatty acids, adiponectin, TNF-α, PAI-1, cytokines
- Muscle
- Liver
- Pancreas
- Vasculature

Fatty acids
Glucose
Fatty acids
Glycerol

Abdominal Obesity

- Adipocytes (esp visceral): proinflammatory endocrine effects
- Increase in free fatty acid deposition in liver
- Intrahepatocyte accumulation of FFA
Adipokines

• **Leptin**: proinflammatory, pro-Insulin resistance (IR)
• **Adiponectin**: anti-inflammatory, anti-IR
• **IL-6**: systemic inflammation, pro-IR, ↑CRP
• **TNF-α**: pro-IR, ↑FFA → ↑TG
• **PAI-1**: ↑ risk thromboembolic events
Adiponectin

- Adipose tissue-specific circulating protein
- Involved in regulation of fat, glucose metabolism
- Decreased adiponectin levels noted in obese subjects and subjects with type 2 diabetes
- Low adiponectin levels associated with reduced HDL-C, hypertriglyceridemia, small dense LDL particles
- Increasing adiponectin levels associated with reduction in body weight and insulin, leading to improved insulin sensitivity
Pathways of Dyslipidemia in Insulin Resistance

Fat Cells → Liver
- ↑ FFA
- ↑ TG
- ↑ ApoB
- ↑ VLDL

Liver → Insulin resistance
- CE
- CETP
- TG

Liver → Kidney
- Hepatic lipase
- ApoA-I
- HDL
- LDL
- Small, dense LDL

CE, cholesteryl esters; FFA, free fatty acids; TG, triglycerides.
Lipid Abnormalities

- High Triglycerides
- Low HDL
- Apo A
- Small dense LDL particles
- Elevated Apo B &/or LDL-Particle #
Metabolic Syndrome

- High Triglycerides
- Low HDL
- Hypertension
- High Glucose
- Increased waist circumference

Prevalence=24% adults in U.S.
# Definitions of Metabolic Syndrome

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<tr>
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</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>IGT, IFG, T2DM, or ins. resistance &amp; 2 of the below</td>
<td>IGT or IFG &amp; any of the below. Clinical judgment</td>
<td>None 3 of the below</td>
<td>None</td>
</tr>
<tr>
<td>Obesity</td>
<td>WHR &gt;0.90 in men or &gt;0.85 in women and/or BMI &gt;30</td>
<td>BMI ≥25</td>
<td>Waist ≥102 cm in men or ≥88 cm in women</td>
<td>Waist (population specific) &amp; any 2 below</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>TG ≥150 and/or HDL-C &lt;35 in men or &lt;39 in women</td>
<td>TG ≥150 and/or HDL-C &lt;40 in men or &lt;50 in women</td>
<td>≥150 or Rx</td>
<td>≥150 or Rx</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>≥140/90</td>
<td>≥130/85</td>
<td>≥130 or ≥85 or Rx</td>
<td>≥130 or ≥85 or Rx</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>IGT, IFG, or T2DM</td>
<td>IGT or IFG (not diabetes)</td>
<td>≥100 or Rx</td>
<td>≥100 or Rx</td>
</tr>
<tr>
<td>Other</td>
<td>Microalbuminuria</td>
<td>Other features of insulin resistance</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
NCEP/ ATP III

• National Cholesterol Education Program
  Adult Treatment Panel III
• Standard guidelines used by MDs
• Focus on identifying early risk & prevention
• New criteria for ‘CardioMetabolic Syndrome’
  – Increased waist/hip ratio
  – Hypertension > 130/85
  – Fasting Glucose >100
  – Elevated Triglycerides > 150
  – Decreased HDL < 40 [m], < 50 [f]
Metabolic Syndrome CV risk

- NHANES III: Individuals over 50 years
- Prevalence of CAD
  - MetSyn or DM: 19.2%
  - Without MetSyn or DM: 8.7%
- ADA: Relative Risk: 3.77 increased CV mortality
Mechanisms of CV risk

- Adipose tissue-endocrine function
- Adipokines: Leptin, Resistin, Adiponectin
- Inflammatory factors: IL-6, TNF alpha, PAI-1, & hs-CRP.
The Causes of Inflammation

• Diet
  – Sugar
  – Trans and saturated fats
  – Polyunsaturated omega 6 oils (except GLA)
  – Insufficient fruits and vegetables

• Stress

• Lack of exercise

• Toxins (metals, petrochemicals)

• Infections – esp. dental

• Obesity/ Insulin Resistance
Antecedents, Triggers and Mediators

- Inflammation
- Genetic propensity
- High Glycemic Diet
- Smoking

Chronic Stress
Visceral Adiposity
Lack of Exercise

Insulin Resistance

Elevated fasting and postprandial Insulin & glucose blood levels
Diabetes Mellitus
Heart Disease

Abdominal Obesity

Inflammation

Insulin Resistance

Dysglycemia
Dyslipidemia
Hypertension
Inflammation and Insulin Resistance
Cause and Effect
Insulin Resistance

- hs-CRP
- IL-6
- IL-8
- TNF alpha
- Leptin
- Resistin
- Adiponectin (inversely)
The Underlying Driver of Progression to Diabetes

Inflammation plays a significant role in the development of insulin resistance and diabetes, particularly in overweight and obese individuals. Adipose tissue (especially visceral) is an active endocrine organ that produces numerous “adipokines”, including inflammatory cytokines. These inflammatory mediators are central to the pathophysiology of obesity and its systemic effects, including insulin resistance, diabetes, atherosclerosis and fatty liver. They also encourage further deposition of visceral fat, thus creating a vicious cycle. Inflammation has been seen to directly correlate with risk of type 2 diabetes.

### Inflammation Markers

<table>
<thead>
<tr>
<th>Marker</th>
<th>Result</th>
<th>Reference Range</th>
<th>Relative Risk for Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>hs-CRP</td>
<td>1.40</td>
<td>&lt; 1.00 mcg/mL</td>
<td>1.75</td>
</tr>
<tr>
<td>Interleukin IL-6</td>
<td>18</td>
<td>&lt; 12 pg/mL</td>
<td>2.57</td>
</tr>
<tr>
<td>Interleukin IL-8</td>
<td>16.0</td>
<td>&lt; 29.2 pg/mL</td>
<td>1.93</td>
</tr>
<tr>
<td>Tumor Necrosis Factor Alpha (TNF-α)</td>
<td>2.0</td>
<td>&lt; 4 pg/mL</td>
<td>1.00</td>
</tr>
<tr>
<td>Plasminogen Activator Inhibitor Type 1 (PAI-1)</td>
<td>150</td>
<td>&lt; 258 ng/mL</td>
<td>2.96</td>
</tr>
</tbody>
</table>

**Average Inflammation Score**: 1.93

* Calculation of Relative Risk Results

**Average Inflammation = 1.0 – 3.02 (range)**

<table>
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<tr>
<th>Score Range</th>
<th>Description</th>
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<tbody>
<tr>
<td>1.00 – 1.50</td>
<td>No/Minimal inflammation</td>
</tr>
<tr>
<td>1.51 – 2.00</td>
<td>Moderate inflammation</td>
</tr>
<tr>
<td>&gt;2.00</td>
<td>Severe inflammation</td>
</tr>
</tbody>
</table>
Type 2 Diabetic Progression & Increased Cardiovascular Risk

- Insulin resistance
- Impaired Glucose Tolerance
- Impaired Fasting Glucose
- Overt type 2 Diabetes
Progression of Insulin Resistance
Progression to Type 2 DM

Tuomilheto-NEJM – May 2001

- 522 subjects with IGT but not DM
- BMI=31 kg/m2
- Follow up 4 years
- Intervention:
  - Diet: low cal, low sat fat, high fiber
  - Exercise
- Weight loss: 5.5 kg vs. 0.8 kg controls
- Intervention 11% DM v 23% DM controls
- Risk of DM reduced 58% w/ intervention
Progression to Type 2 DM

Disease Progression

<table>
<thead>
<tr>
<th>Key</th>
<th>Adiponectin</th>
<th>Insulin</th>
<th>Proinsulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adiponectin</td>
<td>🔄 A</td>
<td>🔄 I</td>
<td>🔄 P</td>
</tr>
<tr>
<td></td>
<td>3.4</td>
<td>2.8</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>&gt; 2.7 mcg/mL</td>
<td>&lt; 5.4 μIU/mL</td>
<td>&lt; 42 pmol/L</td>
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</table>

© 2010
Stage 2: Elevated Fasting Insulin

- Usually due to a combination of insulin resistance and early beta-cell impairment
- 24 million cases of type 2 DM in the U.S., but 57 million cases of ‘pre-diabetes’
- Pattern recognition:
  - LOW Adiponectin
  - HIGH or high-normal HOMA-IR
  - HIGH Insulin, but normal Proinsulin
  - Mildly elevated glucose and/or HbA1C
    - Fasting glucose 100-126 mg/dl and/or 2-hr pp glucose 140-200 mg/dl and/or HbA1C 5.5-6.0%
- Treat with diet, lifestyle, supplementation, possible pharmacotherapy.
Treatment recommendations for Stage 2:

**Lifestyle considerations**
- Reduce weight;
- Increase physical activity (esp. aerobic);
- Reduce stress;
- Treat any inflammatory disorders

**Dietary considerations**
- Avoid sugar and refined carbohydrates, fructose, soft drinks, alcohol, and trans fats. Minimize saturated fats.
- Emphasize a high-fiber, low-saturated fat, Mediterranean-type diet (e.g., legumes and whole grains, fresh fruits and vegetables, nuts & other monounsaturates, foods rich in omega-3 fats, such as cold water fish).

**Supplementation considerations**
- Nutritional: B vitamins, vitamin D, biotin, Mg, Zn, Cr, α-lipoic acid & other antioxidants, flavonoids (e.g., grape seed extract), fish oils, fiber supplement;
- Herbal: Gymnema sylvestre, American Ginseng, Curcumin
- Hormonal: DHEA (if low)

**Medication considerations**
- Insulin sensitizers: Biguanides (e.g., metformin);
- Dual PPAR agonists (e.g., aleglitazar)
- Inhibitors or starch digestion: α-Glucosidase inhibitors (e.g., acarbose)
- Improvement of HOMA: DPP-4 Inhibitors (e.g., sitagliptin) or Pramlintide
## Therapeutic Options

<table>
<thead>
<tr>
<th>Diet &amp; Lifestyle</th>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Stage 3</th>
</tr>
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<tbody>
<tr>
<td>Reduce excess weight by 7%</td>
<td>☐</td>
<td>☐</td>
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<tr>
<td>Increase physical activity (Aerobic/Anaerobic)</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
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<tr>
<td>Stress reduction</td>
<td>☐</td>
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<table>
<thead>
<tr>
<th>Nutraceutical &amp; Botanical Supplements*</th>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Stage 3</th>
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<tbody>
<tr>
<td>α-Lipoic acid [600 - 1200 mg daily]</td>
<td>☐</td>
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<tr>
<td>Omega-3 fatty acids/Fish oils [2 - 6 g daily]</td>
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<tr>
<td>Glucomannan/Soluble fiber [1.2 - 13 g daily]</td>
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<tr>
<td>American ginseng [3 g daily]</td>
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<tr>
<td>β-Glucan/Soluble fiber [15 - 90 g daily]</td>
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<tr>
<td>Chromium [200 - 300 mcg Cr(III) daily]</td>
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<tr>
<td>Gymnema sylvestre [200 mg twice daily]</td>
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</table>

<table>
<thead>
<tr>
<th>Medication</th>
<th>Insulin sensitizers</th>
<th>Inhibitors of starch digestion</th>
<th>Incretins (improve β-cell function)</th>
<th>Insulin secretagogues</th>
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</thead>
<tbody>
<tr>
<td>Biguanides (e.g., Metformin)</td>
<td>☐</td>
<td>☐</td>
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<tr>
<td>Dual PPAR agonists (e.g., Aleglitazar)</td>
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<td>Thiazolidinediones (e.g., Pioglitazone)</td>
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<td>α-Glucosidase inhibitors (e.g., Acarbose)</td>
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<td>Amylin (e.g., Pramlintide)</td>
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<tr>
<td>DPP-4 Inhibitors (e.g., Sitagliptin)</td>
<td>☐</td>
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<tr>
<td>Incretins mimetic (e.g., Exanatide)</td>
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<td>Sulfonylureas (e.g., Glipizide)</td>
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<tr>
<td>Meglitinides (e.g., Nateglinide)</td>
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</table>

* Listed in order of highest to lowest strength of scientific evidence

🔥 Anti-inflammatory effects

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Genova Diagnostics
Innovative Testing for Optimal Health
Weight Loss

Oprah show

• 15-20 lbs weight loss:
• ↓ Leptin, Insulin, IL-6, C-RP, TNF-α
• ↑ Adiponectin
• ↓ TG, Glucose
• ↑ HDL
Weight Loss

Biggest Loser Season 7

• 40-54% body mass

• Adiponectin: 2-3x increase
• Leptin: 47 to 0.73
• Insulin: normalized
• C-RP: < 2 all except one case
Conclusions

• Recognition of magnitude of epidemic
• Societal and physiologic drivers
• Pathophysicsology of obesity
• Cardiometabolic Risk
• Importance of Prevention
Diabetes Mellitus
Heart Disease

Abdominal Obesity

Inflammation

Insulin Resistance

Dysglycemia
Dyslipidemia
Hypertension

Dysglycemia
Dyslipidemia
Hypertension
Questions & Answers

Register for upcoming LiveGDX Webinars online @ www.gdx.net
Welcome to Genova Diagnostics

As part of our continued commitment to medical education, we are excited to continue our new webinar series, "Heart Health". This insightful four-part series continues Wednesday, June 1, 2011, as Chief Medical Officer Patrick Hanaway M.D., presents "New Heart Disease Risk Factors," an in-depth look at how clinical lab testing can provide a thorough assessment of an individual’s cardiovascular health status.

You can register here for any of the remaining "Heart Health" presentations. Registrants who have attended all four parts of the "Heart Health" series will be entered into a drawing for an Apple iPad2™. We look forward to seeing you there.

Hello, Patrick Hanaway.
If you're not Patrick Hanaway, please [click here].

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LiveGDX Webinars

As part of our continued commitment to medical education, Genova Diagnostics is offering monthly webinars to enhance physician understanding of diagnostic tools.

You may register here to participate real time for any of the upcoming LiveGDX presentations.

To view previously recorded LiveGDX webinars, please click on the webinar title below and follow the instructions. Webinars are viewable using most MP4 players such as Quicktime 7 or later and Windows Media Player 12 or later.

Previously Broadcast Webinars

- **Patient’s Progression to Diabetes** Broadcast Date: May 4, 2011 (MPEG-4 video, 40mb - 58 minutes)
- **New Heart Disease Risk Factors** Broadcast Date: June 1, 2011 (MPEG-4 video, 43mb - 63 minutes)
Upcoming LiveGDX Webinars

HeartHealth

12:00 Noon and 8:00 PM EST

• August 3: Genomic Risk of Heart Disease
LearnGDX On-Line Education

Welcome to LearnGDX! Here you will find audio-visual learning modules available 24/7 to help you to understand and clinically apply Genova’s broad array of diagnostic testing. Each learning module links to an extensive library of support materials.

Below you will find the initial top level learning modules. We are currently developing hundreds of additional in-depth LearnGDX modules, extending across all areas of testing to help you meet the needs of your patients.

Enhanced Nutrition Report Design

The following LearnGDX modules are focused on giving clinicians insight into our newly redesigned and enhanced patient results

Report Review

NutrEval
Optimal Nutritional Evaluation - ONE
Metabolic Analysis Profile - MAP
Essential & Metabolic Fatty Acids Analysis
Amino Acids

Case Studies

Fatigue - NutrEval
Depression - NutrEval
Optimal Health - ONE

In-Depth Modules

Antioxidants, Interpretation At-A-Glance
B-Vitamins, Interpretation At-A-Glance
Minerals, Interpretation At-A-Glance
Digestive Support, Interpretation At-A-Glance
Functional Imbalances, Interpretation At-A-Glance
Oxidative Stress - Biomarkers
Metabolic Analysis - Biomarkers
Amino Acids Plasma - Biomarkers
Amino Acids Urine - Biomarkers
THE METABOLIC SYNDROME: Pre-Diabetes, Hypertension and Heart Disease

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