New perspectives on the metabolic syndrome

XXIV Annual Fernandez Cruz Memorial lecture

October 20, 2005

Prof. Gaetano Crepaldi
University of Padua
CNR - Center on Aging, Padua
Outline

- History and definition
- Scientific achievements
- Future challenges
Syndrome X recognised as a disease (ICD #2777.7)

- AACE's request for a new ICD-9-CM code describing Dysmetabolic Syndrome X has been approved by the Centers for Disease Control. The new code, 277.7, is available for use as of October 1, 2001

......but well before we had suggestions from:
"Tulp, in the 17th century, made the connection between hyperlipidemia and the ingestion of saturated fatty acids ("pure milk on the blood"), obesity and bleeding tendency in a patient. Not only that, he suggested a correct therapeutic approach, mainly the reduction of the intake of saturated fatty acids, and, finally, recognized the association between premature atherosclerosis and sudden death."

_Lancet_ 342, 1536, 1993
About 250 years ago, GB Morgagni, Professor of Medicine in the University of Padua, described very clearly in a male patient, the association between visceral obesity, hypertension, bladder stones, and atherosclerosis.
In 1923 Kylin described the co-occurrence of hypertension, hyperglycemia and hyperuricemia.
The Degree of Masculine Differentiation of Obesities:

A FACTOR DETERMINING PREDISPOSITION TO DIABETES, Atherosclerosis, Gout, and Uric Calculous Disease

By Jean Vague, M.D.*

Am J Clin Nutr 4, 56, 1956

Vague J (1947) was the first to identify the importance of “android obesity”, meaning the upper body adiposity as the condition more often associated with diabetes and cardiovascular disease.
The first systematic description of a syndrome was made by Avogaro and myself at the first EASD meeting, in 1965, in Montecatini Terme.
53. Essential hyperlipemia, obesity and diabetes

It has been known for a long time that deranged diabetes with ketosis is characterized by hyperlipemia; that higher values of serum lipids are more frequent in obesity than in normal; and that diabetes is a frequent complication of obesity. Nevertheless there are no available data for a strict pathogenetic relationship among these three metabolic abnormalities. In five patients studied by the authors it has been ascertained: 1) high degree hyperlipemia with enormous increase of serum triglycerides, creamy serum and normal lipoprotein lipase activity; 2) mild or moderate diabetes without ketosis; 3) obesity with an overweight of 25% to 60%. In all patients after a two weeks on a diet, poor in carbohydrate (10-15%), with 2000 cal. per diem, the following have been observed: 1) a body weight loss of between 5 and 15 kg; 2) a drop of blood glucose to normal values; 3) a dramatic decrease of serum triglycerides with a distinct clearing of the serum. These data support the view that in these patients both obesity and hyperlipemia depend upon an increased synthesis of lipid from carbohydrates. The strict dependence of the three metabolic disorders on a dietary carbohydrate intolerance seems to suggest a peculiar syndrome including hyperlipemia, obesity and diabetes. The development of ischemic heart disease and, less frequently, of arterial hypertension is often found in these patients.
The strict dependence of the three metabolic disorders seems to suggest a peculiar syndrome including hyperlipidemia, obesity and diabetes. The development of ischemic heart disease and less frequently of arterial hypertension is often found in these patients.
Association of hyperlipemia, diabetes mellitus and mild obesity

P. Avogaro, G. Crepaldi, G. Enzi, A. Tiengo


all three conditions have been successfully treated with hypocaloric low carbohydrate diet. The results confirm a strict relationship among the three metabolic disorders
suggesting that not only diet, but also physical activity is important in the prevention and treatment of the MetS
# The Plurimetabolic Syndrome

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Obesity (Intra-abdominal)</strong></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Insulin resistance/Diabetes</strong></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Hyperlipidemia</strong></td>
<td></td>
<td></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>✓ TG</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>↑ VLDL</td>
<td></td>
<td></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>↓ HDL</td>
<td></td>
<td></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Hypercoagulability</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td><strong>Increased Uric Acid</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
</tr>
</tbody>
</table>
Reaven, 1988

- In 1988 Reaven introduced the concept of *Sindrome X* as the clustering of disturbances in glucose and insulin metabolism, dyslipidemia and hypertension. Reaven suggested that insulin resistance, with the consequent hyperinsulinemia, underlies this clustering and represents an important cardiovascular disease risk factor per se.

- In 1991, Ferranini also suggested that this clustering was caused by insulin resistance and coined the term of “insulin resistance syndrome”
Diabetes, IFG, IGT, or HOMA insulin resistant and at least two of the following criteria:

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI &gt; 30 kg/m² and/or Waist-to-hip ratio &gt; 0.90 in men or &gt; 0.85 in women</td>
<td></td>
</tr>
<tr>
<td>Serum triglycerides =&gt; 150 mg/dl (1.7 mmol/l) or HDL-C &lt; 35 mg/dl (&lt; 0.9 mmol/l) in men and &lt; 39 mg/dl (1.0 mmol/l) in women</td>
<td></td>
</tr>
<tr>
<td>Blood pressure =&gt; 140/90 mmHg</td>
<td></td>
</tr>
<tr>
<td>Urinary albumin excretion rate =&gt; 20 µg/min</td>
<td></td>
</tr>
</tbody>
</table>
ODDS RATIO FOR METABOLIC SYNDROME, BY GENDER AND BMI

Quartiles BMI:

**Males**
- Q1 < 23.9
- Q2 23.9 - 26.2
- Q3 26.2 - 28.5
- Q4 > 28.5

**Females**
- Q1 < 24.1
- Q2 24.1 - 27.1
- Q3 27.1 - 30.4
- Q4 > 30.4

After adjusting for WC

*ILSA Study, in press*
ODDS RATIO FOR METABOLIC SYNDROME, BY GENDER AND WAIST CIRCUMFERENCE

Quartiles WC:

**Males**
- Q1 < 91
- Q2 91-97
- Q3 97-104
- Q4 > 104

**Females**
- Q1 < 89
- Q2 89-97
- Q3 97-106
- Q4 > 106

After adjusting for BMI

ILSA Study, in press
Fat mass: 19.8 kg
VAT: 155 cm²

Fat mass: 19.8 kg
VAT: 96 cm²
Obesity and HDL cholesterol
Inuit and Europeans

Jorgensen ME. Int J Obesity, 2003
Obesity and blood pressure
Inuit and Europeans

Blood pressure

- Denmark (6,784)
- Greenland (1,108)

Males

Females

Jorgensen ME. Int J Obesity, 2003
### ATP III: The Metabolic Syndrome

<table>
<thead>
<tr>
<th>Risk Factor (≥3)</th>
<th>Defining Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal obesity</td>
<td>Waist circumference*</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>≥150 mg/dl</td>
</tr>
<tr>
<td>HDL-C</td>
<td>&lt;40 mg/dl in men; &lt;50 mg/dl in women</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>≥130/≥85 mm Hg</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>≥110 mg/dl</td>
</tr>
</tbody>
</table>

* Men: >102 cm; women >88 cm

**IDF: The Metabolic syndrome, 2005**

<table>
<thead>
<tr>
<th>Abdominal Obesity</th>
<th>(waist circumference: $\geq 94$ cm European males and $\geq 80$ cm European females, specific values for ethnic groups)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Plus at least two of the following 4 factors:</strong></td>
<td></td>
</tr>
<tr>
<td>triglycerides $\geq 150$ mg/dl ($1.7$ mmol/l) or in treatment</td>
<td></td>
</tr>
<tr>
<td>HDL-C $&lt; 40$ mg/dl ($&lt; 1.03$ mmol/l) in males</td>
<td></td>
</tr>
<tr>
<td>$&lt; 50$ mg/dl ($&lt; 1.29$ mmol/l) in females or in treatment</td>
<td></td>
</tr>
<tr>
<td>Blood Pressure $\geq 130/85$ mmHg or in treatment</td>
<td></td>
</tr>
<tr>
<td>Glycaemia $\geq 100$ mg/dl ($\geq 5.6$ mmol/l)</td>
<td></td>
</tr>
</tbody>
</table>
"Abdominal obesity is the form of obesity most strongly associated with the metabolic syndrome. It presents clinically as increased waist circumference."

"ATP III and IDF recommend that obesity be the primary target of intervention for metabolic syndrome."

Table 2. Frequency of the metabolic syndrome abnormalities according to the two definitions

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th></th>
<th>Women</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>WHO</td>
<td>NCEP</td>
<td>WHO</td>
<td>NCEP</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>20%</td>
<td>13%</td>
<td>22%</td>
<td>22%</td>
</tr>
<tr>
<td>Glucose abnormality</td>
<td>39%</td>
<td>36%</td>
<td>35%</td>
<td>27%</td>
</tr>
<tr>
<td>Insulin resistance</td>
<td>26%</td>
<td>—</td>
<td>32%</td>
<td>—</td>
</tr>
<tr>
<td>Obesity</td>
<td>72%</td>
<td>19%</td>
<td>71%</td>
<td>51%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>21%</td>
<td>36%</td>
<td>23%</td>
<td>35%</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>9%</td>
<td>—</td>
<td>11%</td>
<td>—</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>15%</td>
<td>—</td>
<td>14%</td>
<td>—</td>
</tr>
<tr>
<td>Hypertriglyceridaemia</td>
<td>—</td>
<td>12%</td>
<td>—</td>
<td>13%</td>
</tr>
<tr>
<td>Low HDL cholesterol</td>
<td>—</td>
<td>12%</td>
<td>—</td>
<td>20%</td>
</tr>
</tbody>
</table>

HDL cholesterol, high-density lipoprotein cholesterol.
Overlap of the metabolic syndrome as defined by the NECP or by the WHO. Inuit Study

Whole group $n = 917$

- WHO $n = 190$
- NCEP $n = 165$
- Only WHO $n = 72$
- Only NCEP $n = 47$
- WHO and NCEP $n = 118$

Jorgensen, 2004
The Metabolic Syndrome
Other proposed definitions

WHO
Diagnostic criteria
Insulin resistance
OR
DM / IGT / IFG

Other components
1) Blood pressure
   \[ \geq 140/90 \]
2) Dyslipidemia
3) Central obesity
4) Microalbuminuria
   \textit{(two or more)}
# The Metabolic Syndrome

### Other proposed definitions

<table>
<thead>
<tr>
<th>WHO</th>
<th>EGIR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Main criteria</strong></td>
<td><strong>Main criteria</strong></td>
</tr>
<tr>
<td>Insulin resistance</td>
<td>Hyperinsulinemia</td>
</tr>
<tr>
<td><em>OR</em></td>
<td></td>
</tr>
<tr>
<td>DM / IGT / IFG</td>
<td></td>
</tr>
<tr>
<td><strong>Other components</strong></td>
<td><strong>Other components</strong></td>
</tr>
<tr>
<td>1) Blood pressure ≥140/90</td>
<td>1) Hyperglycemia</td>
</tr>
<tr>
<td>2) Dyslipidemia</td>
<td>2) Blood pressure ≥140/90</td>
</tr>
<tr>
<td>3) Central obesity</td>
<td>3) Dyslipidemia</td>
</tr>
<tr>
<td>4) Microalbuminuria (two or more)</td>
<td>4) Abd. obesity (two or more)</td>
</tr>
</tbody>
</table>
### The Metabolic Syndrome

#### Other proposed definitions

<table>
<thead>
<tr>
<th>WHO</th>
<th>EGIR</th>
<th>AACE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Main criteria</strong></td>
<td><strong>Main criteria</strong></td>
<td><strong>1)</strong> Fasting glucose between 110 and 126 mg/dL or 2-Hour postglucose challenge &gt; 140 mg/dL</td>
</tr>
<tr>
<td>Insulin resistance OR DM / IGT / IFG</td>
<td>Hyperinsulinemia</td>
<td><strong>2)</strong> BP ≥130/85</td>
</tr>
<tr>
<td><strong>Other components</strong></td>
<td><strong>Other components</strong></td>
<td><strong>3)Dyslipidemia</strong></td>
</tr>
<tr>
<td>1) Blood pressure ≥140/90</td>
<td>1) Hyperglycemia</td>
<td><strong>4) Obesity</strong></td>
</tr>
<tr>
<td>2) Dyslipidemia</td>
<td>2) Blood pressure ≥140/90</td>
<td><strong>5) Family history of type 2 diabetes, hypertension or CVD, Polycystic ovary syndrome, Sedentary lifestyle, Advancing age, Ethnic groups having high risk for type 2 diabetes or CVD (clinical judgement)</strong></td>
</tr>
<tr>
<td>3) Central obesity</td>
<td>3) Dyslipidemia</td>
<td></td>
</tr>
</tbody>
</table>
Prevalence of the Metabolic Syndrome in selected countries (EGIR)

**MEN age > 55 years**

- **Barilla**
- **D.E.S.I.R**
- **Ely**
- **Glostrup**
- **Morgen**
- **Viva**
- **Malmö**

**Percent %**

- EGIR
- WHO
Metabolic Syndrome: Prevalence Increases With Age (ATP III)

47 million or 23% of US Adults Have Metabolic Syndrome

Men (n=4265)
Women (n=4559)

Age, yr

Prevalence, %

NHANES III: Age-Adjusted Prevalence of 3 Risk Factors for the Metabolic Syndrome*

*Criteria based on ATP III; diabetics were included in diagnosis; overall unadjusted prevalence was 21.8%.

PREVALENCE (%) OF THE METABOLIC SYNDROME.
THE ILSA STUDY

(p<0.0001)

Maggi & Crepaldi, J Gerontol, 2005
PREVALENCE (%) OF COMPONENTS OF METABOLIC SYNDROME. ILSA Study

Maggi & Crepaldi, J Gerontol, 2005

*: (p<0.0001)
Men, nondiabetic

Factor 1: BMI, WC, WHR

Factor 2: CH, APO B, SBP, DBP

Men, diabetic

Factor 1: WHR, TG, HDL, WC

Factor 2: Fasting glycemia, HbA1c

Factor 3: SBP, DBP

Noale and Crepaldi, Atherosclerosis, 2005
Women, nondiabetic

- **factor 1**: BMI, WC, WHR
- **factor 2**: TG, CH, APO B
- **factor 3**: SBP, DBP

Women, diabetic

- **factor 1**: BMI, INS, HDL, APO A
- **factor 2**: TG, CH, APO B
- **factor 3**: SBP, DBP
- **factor 4**: WHR, GLYCEMIA, HbA1C

Noale and Crepaldi, Atherosclerosis, 2005
Prevalence of the Metabolic Syndrome according to WHO definition

Age range
- 46-68
- 60
- 40-81M;40-55F
- 30-79
- 30-79
- 35+
- 30-79
- 50-69
- 35-64
- 25+

Zimmet, 2004
Prevalence of the Metabolic Syndrome according to ATP III definition

Zimmet, 2004

*Obesity criteria adjusted to waist circumference appropriate for an Indian population
Definition of the Metabolic Syndrome – have we reached the end of the road?

- Defining insulin resistance
- Defining obesity
- Defining glucose intolerance
Defining insulin resistance

- Hyperinsulinemic euglucemic clamp
- Fasting insulinemia
- HOMA IR
Defining glucose intolerance

✓ Defining obesity

Defining insulin resistance
Defining obesity in the Metabolic Syndrome

- **WHO**
  - WHR > 0.9 for men
  - WHR > 0.85 for women
  - or
  - BMI > 30 kg/m²

- **EGIR**
  - Waist circumference ≥ 94 cm for men
  - ≥ 80 cm for women

- **ATPIII**
  - Waist circumference ≥ 102 cm for men
  - ≥ 88 cm for women

- **IDF**
  - Waist circumference:
    - ≥ 94 cm European males
    - ≥ 80 cm European females
    - (specific values for ethnic groups)

ECE 2003
Definition of the Metabolic Syndrome – have we reached the end of the road?

Defining insulin resistance

Defining obesity

✓ Defining glucose intolerance
Defining glucose intolerance in the Metabolic Syndrome

- **WHO**
  - Fasting p-glucose ≥ 6.1 mmol/l (110 mg/dl) (IFG+DM)
  - 2-h p-glucose ≥ 7.8 (140 mg/dl) (IGT + DM)
  - Known diabetes

- **EGIR**
  - Fasting p-glucose ≥ 6.1 (IFG, no DM)

- **ATPIII**
  - Fasting p-glucose ≥ 6.1 mmol/l (IFG+DM)

- **IDF**
  - Fasting glycaemia ≥ 100 mg/dl (≥ 5.6 mmol/L)
Quartiles glycemia:

**males**
- Q1 < 90
- Q2 90-98
- Q3 98-110
- Q4 > 110

**females**
- Q1 < 88
- Q2 88-96
- Q3 96-108
- Q4 > 108
Have we reached the end of the road?

No!
Metabolic Syndrome and atherosclerosis
Metabolic Syndrome and Atherosclerosis

Metabolic Syndrome
- Intra-Abdominal Obesity
- Hyperinsulinemia/Diabetes
- Hypertriglyceridemia
- Low HDL-C
- Small, dense LDL
- Hypertension
- Hypercoagulability
- ↑ Uric Acid

Atherosclerosis
How could central obesity contribute to Syndrome X?

Apo B  Glucose  Insulin
↑TG

Liver

Insulin resistance (IR)

NEFAs

PAI-1

IL-6 adiponectin
TNF-α

Coronary artery
- Thin fibrous cap
- Unstable plaque
- Impaired fibrinolysis
- Increased collagen
- Endothelial dysfunction

Inflammatory factors

Glucose

Expanded Internal fat

NEFAs

Skeletal Muscle

Adapted from Després et al.
New markers of CHD risk: what to look for?

- **Atherogenic dyslipidemia**
  - ↑ Triglycerides
  - ↓ HDL-cholesterol
  - ↑ Cholesterol/HDL-cholesterol ratio
  - "Normal" LDL-cholesterol but ↑ apo B
  - Small, dense LDL and HDL
  - Postprandial hyperlipidemia

- **Insulin resistance**
  - Insulin resistance
  - Hyperinsulinemia
  - Hyperglycemia
  - Type 2 diabetes

- **Thrombotic state**
  - ↑ PAI-1
  - ↑ Fibrinogen

- **Inflammatory state**
  - ↑ CRP
  - ↑ Cytokines

- **Abdominal obesity**
- **Metabolic risk factors**

- **Inflammation**
- **Lipid core**
- **CORONARY ATHEROSCLEROSIS**
- **UNSTABLE PLAQUE**

- ↑ risk of acute coronary syndrome

Adapted from Despres, 2004
Mechanisms Relating The Metabolic Syndrome and Dyslipidemia

IA Fat Cells

Liver

IA Fat Cells

Liver

HDL

LDL

LDL

VLDL

VLDL (hepatic lipase)

Apo A-1

Kidney

Insulin

FFA

IR

↑ TG

↑ Apo B

↑ VLDL

↑ hepatic lipase

↑ hepatic lipase

↑ Small Dense LDL

↑ TG

(CETP)

(CETP)

(CETP)
Metabolic Syndrome and Atherosclerosis

Intra-Abdominal Obesity
Hyperinsulinemia/Diabetes
Hypertriglyceridemia
Small, dense LDL
Low HDL
Hypertension
Hypercoagulability
↑ Uric Acid

Metabolic Syndrome

Atherosclerosis
Frequency of different Forms of Dyslipidemia in men with Coronary Artery Disease

Frequency (%)

FH, Low HDL, FCHL, Apo E3/E4, Homocys, Lp(a), ALP

ALP: ↑TG
     ↓HDL-C
     Small, dense LDL

(Superko, Circulation, 1996)
Increased Dyslipidemia in the Plurimetabolic Syndrome

- Triglycerides
- VLDL
- small dense LDL
- Apo B

Decreased

- HDL-C
- Apo A-I
Relation Between Insulin Resistance and Hypertriglyceridemia

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

Association Between Hyperinsulinemia and Low HDL-C

Association of Small, Dense LDL With Insulin Resistance

Steady-state plasma glucose

Glucose (mmol/L)

Pattern A (Big, Buoyant LDL)  Intermediate pattern  Pattern B (Small, dense LDL)

LDL Atherogenicity

- Plasma LDL particle number
- LDL particle size and density

Low Risk of CAD

Big, buoyant LDL

Hepatic Lipase

Small, dense LDL

High Risk of CAD
Increased susceptibility to oxidation

Increased vascular permeability

Conformational change in apo B

Decreased affinity for LDL receptor

Association with insulin resistance

Association with high TG and low HDL (ALP)

LDL Density and Presence of Macrophages in the Carotid Plaque

LDL Buoyancy (Rf)

Macrophages (n°/unit of area)

r = -0.639
p < 0.0005

(A. Zambon and G. Crepaldi, JACC 2002)
**Small, dense LDL**

SM-E7 smooth muscle cells

**Big, buoyant LDL**

SM-E7

HAM56 macrophages

- ap
- m

- ap
- m
Cerebrovascular Events and Small, Dense LDL

Yes CV Events: n=50
No CV Events: n=18

# Patients

χ² = 9.53; p=0.002

(A.Zambon and G.Crepaldi, JACC 2002)
Metabolic Syndrome, Atherosclerosis

Metabolic Syndrome
- Intra-Abdominal Obesity
- Hyperinsulinemia/Diabetes
- Hypertriglyceridemia
- Low HDL-C
- Small, dense LDL
- Hypertension
- Hypercoagulability
- ↑ Uric Acid

Atherosclerosis
Factors Promoting Thromboembolic Disease in The Plurimetabolic Syndrome

- Increased plasma fibrinogen
- Increased plasminogen activator inhibitor 1
- Increased platelet aggregability
- Increased hs-CRP levels

CRP LEVELS AND COMPONENTS OF METABOLIC SYNDROME
(Women’s Health Study, n=14719)

- Insulin Resistance/Diabetes
- Visceral Obesity
- Hypertension
- HyperTG
- Low HDL-C

(N=4086) (N=3884) (N=3152) (N=2292) (N=1135) (N=170)
Genetic Factors in Metabolic Syndrome

Genetic factors contribute to:

- Obesity
- Atherogenic dyslipidemia (high TG, high apo B, small LDL, low HDL)
- Hypertension
- Hyperglycemia
- Proinflammatory state
- Prothrombotic state
Clustering of Risk Factors Incorporated into the Metabolic Syndrome

Includes risk factors not routinely measured

- Insulin resistance
- Small dense LDL
- Endothelial dysfunction
- Abnormal sympathetic nervous activity
- Prothrombotic markers—PAI-1, fibrinogen
- Proinflammatory markers such as CRP; VCAM
The Metabolic Syndrome: issues to be addressed

- Are there other components we should be measuring (e.g. NASH)?
- What is the optimum method for diagnosis?
- Should there be ethnic specific criteria?
recommendations to clinicians are:

Adults with any major CVD risk factor should be evaluated for the presence of other CVD risk factors.

Patients with CVD risk variables above the cut point for normal should receive counseling for lifestyle modification, and at cut points indicative of frank disease (e.g., blood pressure >140/90 mmHg, fasting plasma glucose >7.0 mmol/l), treatment should correspond to established guidelines.

Providers should avoid labeling patients with the term "metabolic syndrome," as this might create the impression that the metabolic syndrome denotes a greater risk than its components, or that it is more serious than other CVD risk factors, or that the underlying pathophysiology is clear.

All CVD risk factors should be individually and aggressively treated.

Until randomized controlled trials have been completed, there is no appropriate pharmacological treatment for the metabolic syndrome, nor should it be assumed that pharmacological therapy to reduce insulin resistance will be beneficial to patients with the metabolic syndrome.
In a 2004 paper, Deen argued forcefully for bringing the concept of metabolic syndrome to the attention of primary care patients. "Metabolic syndrome is a prototype of the way in which we can now identify those patients who are at highest risk of bad outcomes. The term is an important way to educate patients about the connection between their lifestyle, health risks, and medical outcomes" Deen says. "It's vitally important for physicians to begin communicating that information to patients."