Metabolic Syndrome

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Objectives

- Be able to outline the pathophysiology of the metabolic syndrome
- Be able to list diagnostic criteria for the metabolic syndrome
- Be familiar with laboratory tests useful for the diagnosis and monitoring of the metabolic syndrome

Outline

- Introduction
- Pathophysiology
- Laboratory testing
- Chronic kidney disease
- Exercise
- Non-alcoholic fatty liver disease
- Conclusions

★ **Table 3**

Partial Listing of Diseases/Conditions/Syndromes Afflicting Each Group of Individuals

Children/Adolescents	Baby Boomers	Geriatrics
Obesity	Obesity	Obesity
Diabetes	Diabetes	Diabetes
Hypertension	Hypertension	Hypertension
Malignant neoplasms	Malignant neoplasms	Malignant neoplasm
Cardiovascular diseases	Cardiovascular diseases	Cardiovascular diseases
Nephritis and nephrosis	Nephritis and nephrosis	Nephritis and nephrosis
Septicemia	Septicemia	Septicemia
Chronic lower respiratory diseases	Chronic lower respiratory diseases	Chronic lower respiratory diseases
Pneumonia/influenza	Pneumonia/influenza	Pneumonia/influenza
Cerebrovascular diseases	Cerebrovascular diseases	Cerebrovascular diseases
	Substance abuse	Substance abuse
	Metabolic syndrome	Stroke
	Polycystic ovary(ies)	Dementia/Alzheimer
	Lung disease(s)	Prostate disease
	Anxiety	Osteoporosis
	Depression	Post-menopause
	AIDS	Pain perception
	Gout	Overactive bladder
	Chronic liver disease(s)	Vitamin B12 deficiency
		Acute alcoholism
		Incontinence

Metabolic Syndrome

- What is it?
  - Constellation of clinical and laboratory findings resulting from central obesity and insulin resistance
- aka cardiometabolic syndrome, dysmetabolic syndrome X, syndrome X
- 47 to 60 million Americans have metabolic syndrome
- At increased risk for:
  - Diabetes mellitus
  - Coronary heart disease
  - Stroke

Diagnostic Criteria

Criterion	NCEP ATP III	WHO 1999	IDF 2005
Central obesity	W >40 in M W >35 in F	W:H >0.9 M W:H >0.85 F	>37 in M * >31 in F
Fasting glucose	>100 mg/dL	≥120 mg/dL *	≥100 mg/dL
Blood pressure	>130/85 or Rx	≥140/90 or Rx	≥130/85 or Rx
Fasting TGs	≥150 mg/dL	≥150 mg/dL	≥150 mg/dL
HDL-C	<40 mg/dL M <50 mg/dL F	≤35 mg/dL M ≤39 mg/dL F	<40 mg/dL M <50 mg/dL F

WHO microalbuminuria ≥30 mg/g

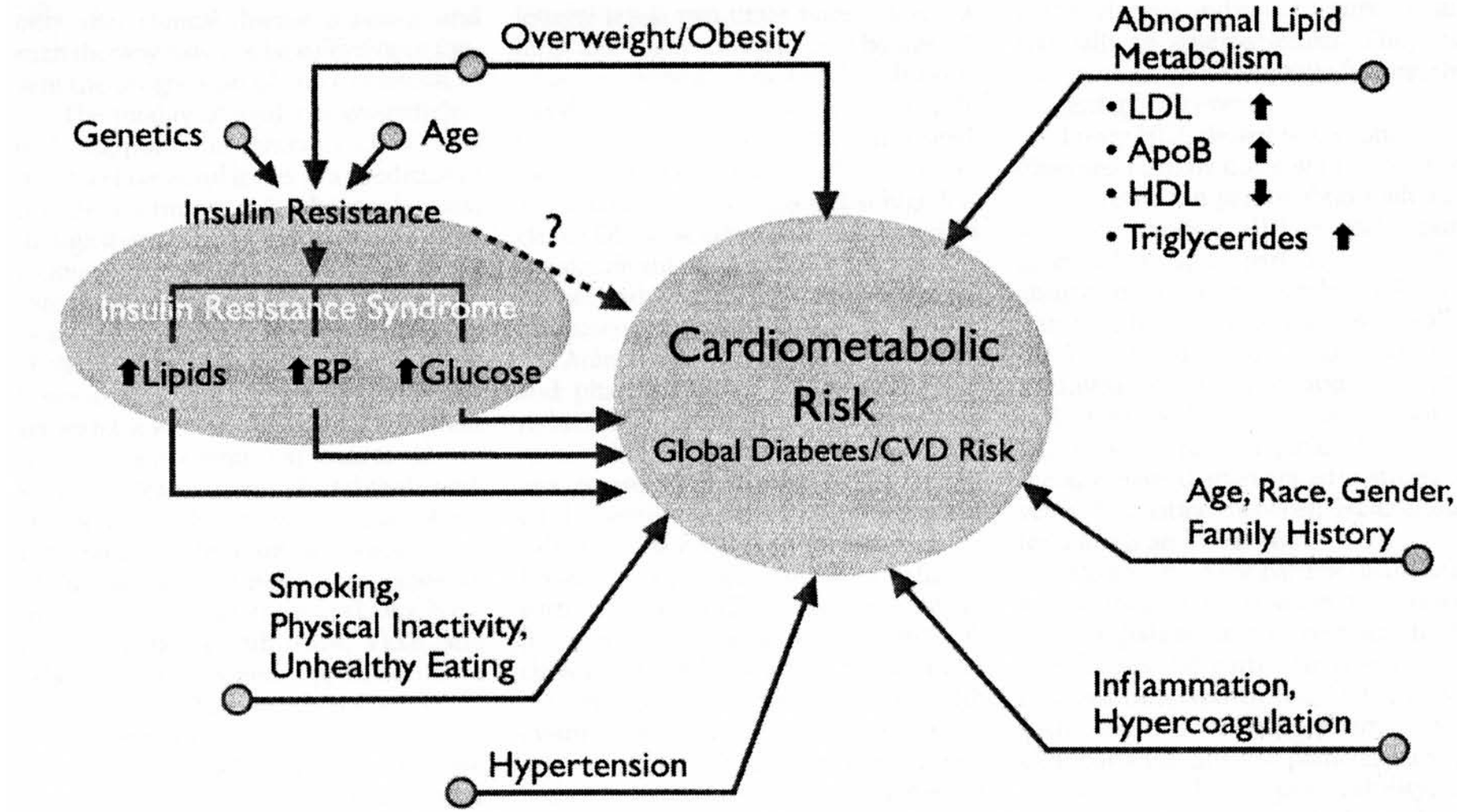
Controversy about Metabolic Syndrome

- AHA contends recognizing metabolic syndrome will help clinicians prevent CVD
- ADA contends metabolic syndrome does not exist as a medically definable syndrome
  - Clinical treatment of syndrome is no different than treating individual components
  - Each risk factor has different degrees, everyone with metabolic syndrome does not have the same risk

Metabolic Syndrome as Predictor of CVD

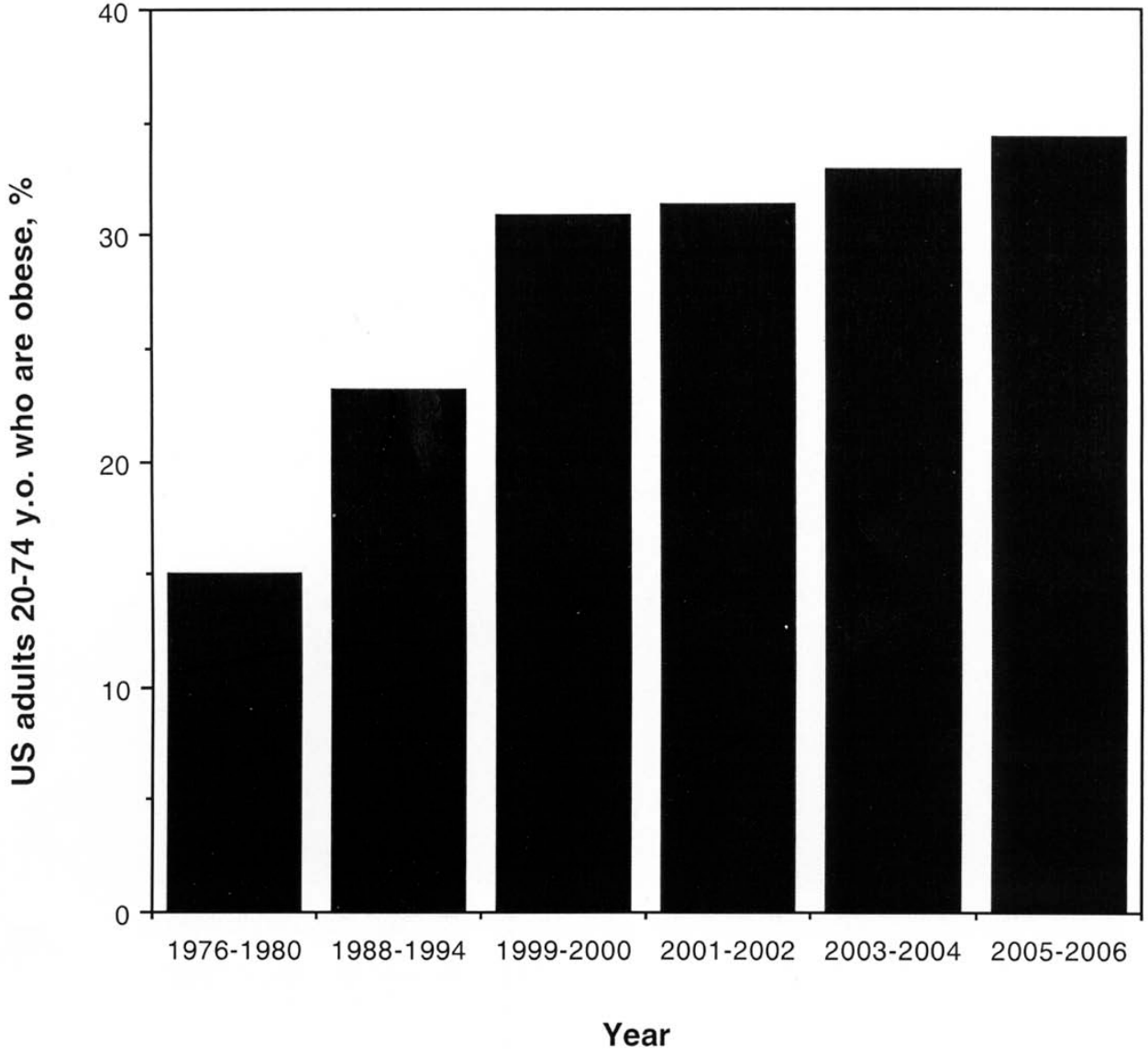
- In the Framingham study, metabolic syndrome alone predicted 25% of all new onset CVD
- In the absence of diabetes, metabolic syndrome did not raise 10 year risk of CVD to >20%--the threshold for ATP III's CHD risk equivalent
- Ten year risk in men with metabolic syndrome was 10-20%
- Ten year risk for women was lower but they were younger

Factors Contributing to Cardiometabolic Risk



Brunzell JD, et al. Diabetes Care 2008;31:811-22.

Obesity in the US



Obesity and Abnormal Body Fat Distribution

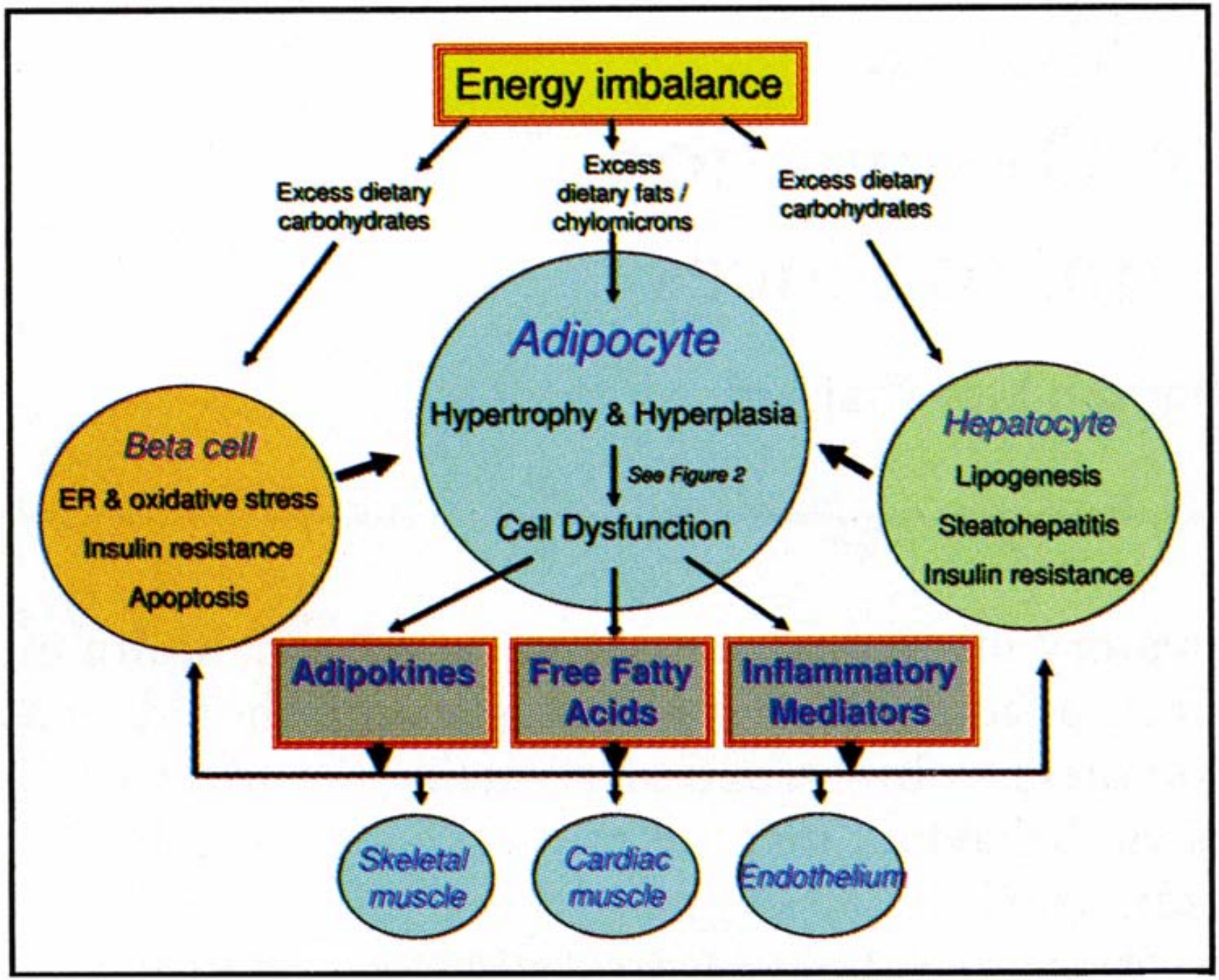
- Obesity epidemic mainly responsible for rising prevalence of metabolic syndrome
- Obesity contributes to
  - Hypertension
  - Elevated serum cholesterol (VLDL)
  - Decreased serum HDL-cholesterol
  - Hyperglycemia

Abdominal Obesity

- Form of obesity most strongly associated with metabolic syndrome and CVD risk
- Presents clinically as increased waist circumference
  - BMI can also be used, but may be less specific
  - Weight lifters have increased BMI, but usually not abdominal obesity

Products of Excess Adipose Tissue

- Non-esterified fatty acids (NEFA)
  - Overloads muscle and liver with lipid, enhances insulin resistance
- PAI-1
  - Contributes to pro-thrombotic state
- Adiponectin
  - Low adiponectin (seen in obesity) correlate with worsening of metabolic risk factors
- Pro-inflammatory cytokines
  - Increase CRP, fibrinogen, and other acute phase reactants



de Ferranti S & Mozaffarian D, Clin Chem 2008;54: 945-55

Insulin Resistance

- Present in majority of people with metabolic syndrome
- Correlates with CVD risk
- Mechanisms underlying link to CVD uncertain
- Insulin resistance may manifest as glucose intolerance
- Many investigators place a greater priority on insulin resistance than obesity
- Insulin resistance increases with increasing body fat content
- A broad range of insulin sensitivities exist at any given level of body fat

Insulin Resistance and BMI

- Body mass index (BMI) $\geq$30 kg/m^2 is associated with postprandial hyperinsulinemia
- BMI 25 to 29.9 show spectrum of insulin resistance
- BMI <25 kg/m^2 is associated with insulin resistance in some populations (South Asians)
- High prevalence of DM and premature CVD in South Asians associated with primary insulin resistance
- Weight gain enhances insulin resistance in primary insulin resistance

Consequences of Hyperinsulinism

- Premature atherosclerosis
- Elevated blood pressure
- Hyperandrogenism—ovarian androgen secrection
- Hyperuricemia
- Major cause of PCOS
- Dylipidemia
  - Hypertriglyceridemia
  - Low HDL-cholesterol
  - Increased LDL particle number
- Fatty infiltration of liver (NAFL→NASH→cirrhosis→HCC)

Metabolic Syndrome Predicts Diabetes

- Risk of new onset diabetes mellitus examined in Framingham cohort
- In men and women the presence of metabolic syndrome was highly predictive
- Nearly half of population attributable risk for diabetes was explained by the presence of ATP III metabolic syndrome

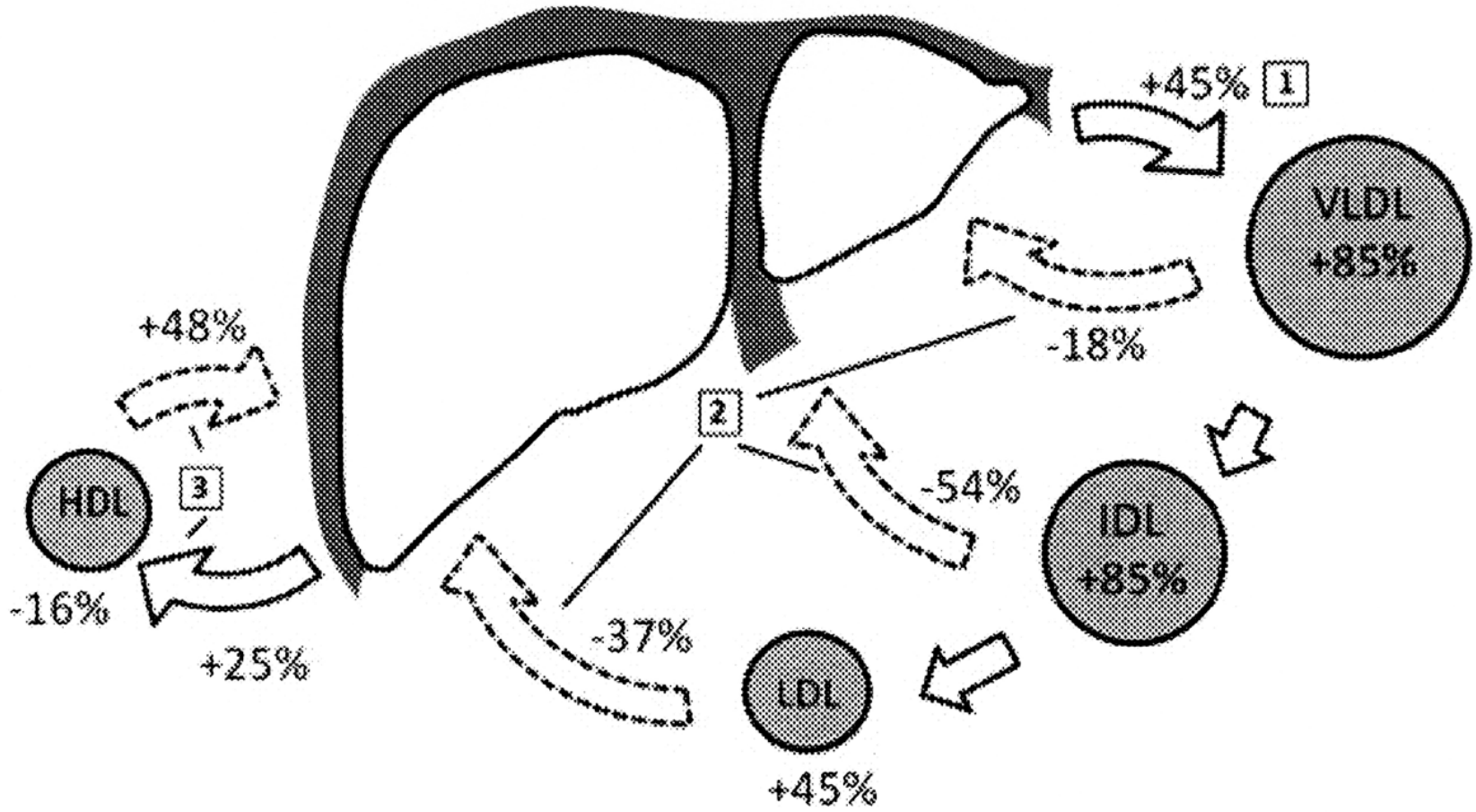
Prevention/Delay of Type 2 DM

- Patients with IFG or IGT
  - Weight loss of 5-7% body weight can prevent DM
  - Increased physical activity 150 min/week walking
- In addition to lifestyle counseling, metformin may be considered if both
  - Combined IFG and IGT plus other risk factors
  - Obese (BMI >30 kg/m^2) and under 60 yrs old

Atherogenic Dyslipidemia

- Elevated fasting triglycerides concentration
- Low HDL-cholesterol concentration
- Increased VLDL & remnant lipoprotein concentrations
- Increased apolipoprotein B concentration
- Increased number of LDL particles
- Small LDL particles
- Small HDL particles

Lipoprotein Metabolism in Metabolic Syndrome



Adiels M et al. Arterioscler Thromb Vasc Biol 2008;28:1225-1236

Elevated Blood Pressure

- Associated with obesity
- Commonly occurs in insulin resistance
- Multifactorial in origin
- Arterial stiffness contributes to systolic hypertension in the elderly

Pro-inflammatory State

- Recognized clinically as elevated C-reactive protein (CRP)
- Commonly present in metabolic syndrome
- One cause is obesity—adipose tissue release IL-6 which stimulates the liver to produce CRP

JUPITER Trial

- LDL-C <130 mg/dL
- CRP ≥2 mg/L
- Randomized to a statin or placebo
- Followed for 3 years
- Trial ended early due to benefits of statins in this group
  - Decreased rate of first major cardiovascular event
  - Decreased rate of death from any cause

Ridker PM et al. NEJM 2008;359:2195-2207.

Hs-CRP and Metabolic Syndrome

- 14,719 women followed for 8 years, 24% had MS
- Outcomes—MI, CVA, CABG/PTCA, cardiac death
- CRP strongly correlated with number of MS criteria
  - 0.7, 1.1, 1.9, 3.0, 3.9, 5.8 mg/L median CRP for 0-5 MS criteria
- At all levels of MS severity, CRP added information
  - CRP <3 mg/L 3.4 per 1000 incidence of event
  - CRP >3 mg/L 5.9 per 1000 incidence of event
- CRP increases PAI-1 expression in aortic endothelial cells

Useful Laboratory Tests

- Apolipoprotein B
- Creatinine
- Fasting triglycerides
- Fasting glucose
- HDL-cholesterol
- Hs-CRP
- LDL-cholesterol
- LDL particle number
- Non-HDL cholesterol
- Urine albumin

Lipoprotein Subclasses and MS

- Subjects with insulin resistance/metabolic syndrome tend to have dyslipidemia:
  - Increased large VLDL particle concentrations
  - Increased small LDL particle concentrations
  - Decreased large HDL particle concentrations
- Small dense LDL particles (B phenotype) is associated with increased cardiovascular risk
- The apolipoprotein B (apo B) concentration reflects number of LDL particles
- Treatments targeting this dyslipidemia may be beneficial

Lipoprotein Management

- LDL-cholesterol
- LDL particle number
  - Better predictor than LDL-C
  - More data needed across ethnicities and ages
- Non-HDL-cholesterol
  - Better predictor than LDL-C
  - Useful in hypertriglyceridemia as secondary target
- ApoB-100
  - Single molecule in each atherogenic particle
  - Better predictor than LDL-C

Lipid Treatment Goals

	LDL-C (mg/dL)	Non-HDL-C (mg/dL)	ApoB (mg/dL)
1) Known CVD or 2) DM plus one or more additional CVD risk factors	<70	<100	<80
1)No DM or known CVD but 2 or more additional risk factors or 2) DM but no other major CVD risk factors	<100	<130	<90

Brunzell JD et al. Diabetes Care 2008;31:811-22.

Chronic Kidney Disease

- The persistent and usually progressive reduction in glomerular filtration rate (GFR less than 60 mL/min/1.73 m^2), and/or
- Albuminuria (more than 30 mg of urinary albumin per gram of urinary creatinine)

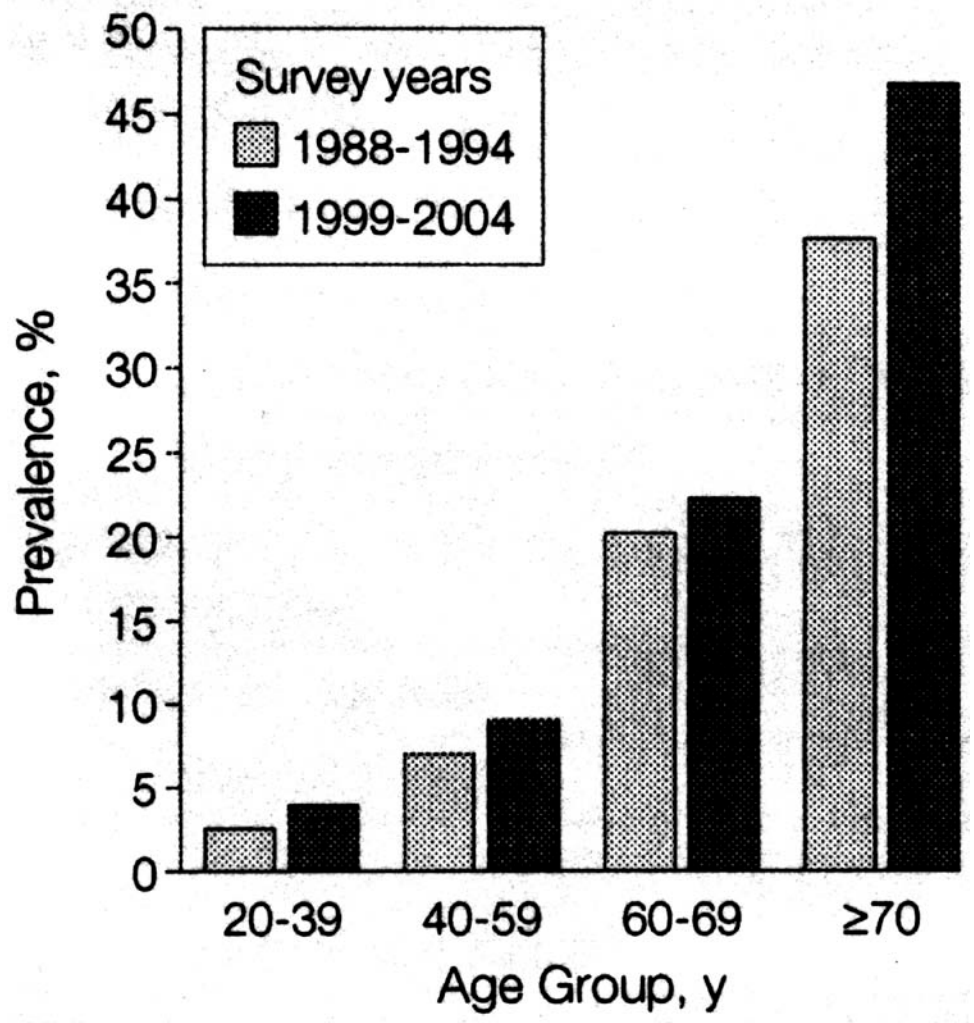
Cardiovascular Disease is Linked to CKD

- Annual mortality from CVD is increased 10 - 100 times with kidney failure
- Risk of CVD is increased 1.4 - 2.05 times with creatinine >1.4 - 1.5 mg/dL
- Risk of CVD is increased 1.5 - 3.5 times with microalbuminuria >30 mg/g

Who is at Risk for Chronic Kidney Disease?

- Diabetes and high blood pressure are the leading causes of kidney failure.
- Individuals with a family history of kidney failure are also at risk.
- Chronic kidney disease may also result from:
  - Hereditary factors, such as polycystic kidney disease (PKD)
  - A direct and forceful blow to the kidneys
  - Prolonged consumption of some over-the-counter painkillers that combine aspirin, acetaminophen, and other medicines such as ibuprofen

Kidney Disease Prevalence Increases with Age



Coresh J, et al. JAMA 2007;298:2038-47.

Limitations of MDRD eGFR

- Validated for adults 18-70 years of age
- Not validated for hospitalized patients
- Not as accurate for eGFR >60 mL/min/1.73 m^2
- Not as accurate when patient's basal creatinine production is very abnormal
  - Patients of extreme body size or muscle mass (e.g., obese, severely malnourished, amputees, paraplegics or other muscle-wasting diseases)
  - Unusual dietary intake (e.g., vegetarian, creatine supplements).

Urinary Albumin/Creatinine Ratio

- A single cutoff (30mg/g) is used
- Age, gender, and race may affect cutoff
- No uniformity in sample type
  - First morning void vs. true random
  - Diurnal, postural, exercise influences
  - Sample handling
    - Non-specific binding to collection container
    - Degradation during storage and freeze-thaw

Who should be Tested for CKD?

- Microalbumin and eGFR
  - All individuals with hypertension—at diagnosis and every 3 years if normal
  - Diabetes mellitus—every year
  - Family history of CKD, every 3 years if normal
  - Those with CVD or increased risk of CVD
- eGFR
  - All individual >65 years old

Exercise and the Metabolic Syndrome

- Regular exercise can help prevent diabetes mellitus
- Exercise can:
  - Lower blood glucose
  - Improve insulin action
  - Contribute to weight loss
  - Reduce risk for cardiovascular disease
- Sedentary lifestyles linked to 23% of deaths from heart disease and diabetes mellitus
- 30 minutes/day of walking can be beneficial
- Strength and endurance training can both be beneficial

Effects of Lifestyle Modifications on Metabolic Syndrome

Metabolic Syndrome Component	Effect of Regular Exercise[a]	Effect of Chronic Caloric Restriction[b]
Waist circumference, cm (%)	–3 to –7 (6)	–4 to –7 (–6)
Triglycerides, mmol/L (%)	–0.21 (–12)	–0.12 (–6)
HDL cholesterol, mmol/L (%)	+0.05 (+4)	+0.07 (+6)
Fasting plasma glucose, mM (%)		
Nondiabetic subjects	Negligible	Negligible
Diabetic subjects	–1.5 (–15)	–1.2 (–15)
Blood pressure, mmHg		
Systolic	–4	–5
Diastolic	–3	–4

Moderate intensity exercise 3-5 days/wk, 30-60 min/day
Modest daily caloric restriction (500-700kcal)

Janiszewski PM et al Am J Lifestyle Med 2008;2:99-108

Non-alcoholic Fatty Liver Disease (NAFLD)

- Nearly one third of American adults
- 70% of patients with diabetes mellitus
- Central adiposity and insulin resistance contribute in both men and women
- Can progress to non-alcoholic steatohepatitis, cirrhosis, fibrosis, and hepatocellular carcinoma

Diagnosis of NAFLD

- LFTs
  - Mild elevations of ALT and GGT
- Ultrasound
- CT
- MRI
- Liver biopsy—definitive diagnostic test

Conclusions

- CVD is the primary clinical outcome of metabolic syndrome
- ATP III criteria identify patients at increased risk for CVD
- Metabolic syndrome confers increased risk for DM
- The liver plays a central role in the metabolic syndrome
- Therapeutic lifestyle changes with emphasis on exercise and weight reduction constitute first line therapy

General References

- Grundy et al. Definition of metabolic syndrome. Circulation 2004;109:433-8.
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- JAMA 2001;285:2486-97. Daniels SR et al. Lipid screening and cardiovascular health in children. Pediatrics 2008;122:198-208.
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