Metabolic Syndrome

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Metabolic Changes Observed in Obesity

- The metabolic abnormalities of obesity reflect molecular signals originating from the increased mass of adipocytes
- The predominant effects of obesity include-
  - dyslipidemias
  - glucose intolerance
  - and insulin resistance
  - hypertension

Metabolic Syndrome

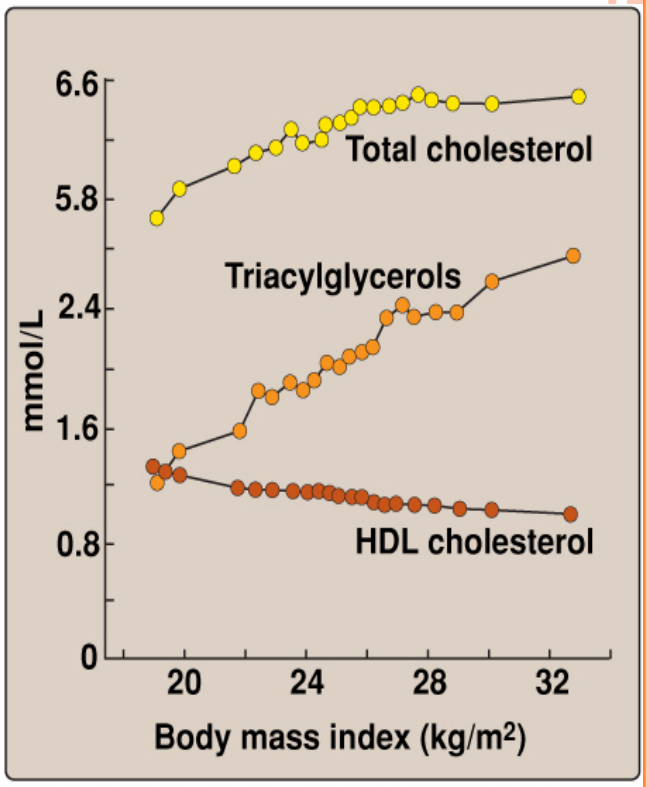
- A cluster of closely related medical conditions which increase the risk of developing heart disease and diabetes
- Features comprising Metabolic Syndrome
  - Obesity (specifically visceral)
  - High serum TGs
  - Low HDL cholesterol
  - Hypertension
  - Hyperglycemia
  - Hyperinsulinemia (insulin resistance)

Effects of Insulin Resistance

- Hydrolysis of stored TGs or fats, leading to elevation of plasma FFA
- Reduction of glucose uptake or glucose utilization among muscle cells and reduction of glycogenesis- both lead to hyperglycemia
- Compensatory hyperinsulinemia causes down regulation of insulin receptors.

Dyslipidemia

- Insulin resistance in obese individuals leads to
  - increased production of insulin in an effort by the body to maintain blood glucose levels
  - causes increased activity of hormone-sensitive lipase, resulting in increased levels of circulating fatty acids
- These fatty acids are carried to the liver and converted to TGs and cholesterol
- Excess TGs and cholesterol are released as VLDL, resulting in elevated serum triacylglycerols
- Concomitantly, HDL levels are decreased.



Dyslipidemia and the MetS an inseparable couple?

- Dyslipidemia is an early and consistent component of insulin resistance
- Liver fat seems to be the unifying factor between dyslipidemia and insulin resistance

Risk Factors for Metabolic Syndrome

- Obesity
- Alcoholism
- Sedentary Lifestyle
- Smokers
- Hypercorticolism (e.g. steroid use or Cushing's disease)
- Drugs (Rifampicin, Isoniazid etc)
- Mutation of insulin receptors

Metabolic Syndrome is Linked to:

- Heart disease
  - 1 .5 - 3 fold increase for atherosclerotic CVD
- Type 2 Diabetes Mellitus
  - 5 fold increase
- Kidney disease
- Reproductive abnormalities in women
  - PCOS, difficulty with ovulation and fertility, irregular periods

Metabolic Syndrome is Linked to:

- Nonalcoholic steatohepatitis (fatty liver)
  - Related to distorted lipid metabolism
- Cancer
  - Obesity is major risk factor for cancer of the esophagus; colon and rectum; liver; gall bladder etc
  - Being overweight and obese accounts for 14% of all cancer deaths in men and 20% of those in women

Diagnosis – WHO criteria (1999)

- Impaired glucose tolerance; DM or insulin resistance ; along with at least two of the below mentioned components

Component	Criterion
Hypertension	BP >140/90 mmHg
Dyslipidemia	High plasma TGs (>1.7mmol/L) Low HDL cholesterol (men <0.9, women <1.0 mmol/L)
Central or Genenral obesity	Waist to hip ratio >0.9 in men, >0.85 in women And/or BMI >30
Microalbuminuria	Urinary albumin excretion rate ≥ 20ug/min or albumin:creatinine ratio ≥ 30mg/g

NCEP* ATP** III Guideline (2002)

Diagnosis: ≥ 3 of these risk factors are present

- Waist circumference:
  - Men>102 cm (>40 in)
  - Women>88 cm (>35 in)
- Triglycerides >150 mg/dL
- HDL cholesterol:
  - Men<40 mg/dL
  - Women<50 mg/dL
- Blood pressure 130/ 85 mm Hg
- Fasting glucose >100 mg/dL

*National Cholesterol Education Programme

** Adult Treatment Panel

Markers of Metabolic Syndrome

- Lipoproteins- LDL, HDL
- Adipokines-
  - Leptin
  - Adiponectin
- Inflammatory markers- CRP, TNF-a, IL-6, IL-8
- Hemostatic marker – Plasminogen Activator inhibitor-1

Current Treatments

- Statins
- Metformin
- Fibrates
- Thiazolidinediones (TZDs)
- Aspirin therapy

Managing Metabolic Syndrome

- Primary intervention: Lifestyle changes
  - Weight reduction (strive for BMI less than 25)
    - Reduced caloric intake and dietary fat
    - Increased physical activity
    - Set realistic goals: 5-10% weight loss from baseline
  - Smoking cessation

Managing Metabolic Syndrome

- Secondary intervention: Pharmacotherapy (for existing risk factors)
  - Management of
    - blood pressure (anti-hypertensives)
    - Lipids (statins, fibrates)
    - Blood glucose (metformin, TZDs)
  - Aspirin for CVD prevention

Lowering Blood pressure

Modification	Recommendation	Average drop on SBP
Weight Loss	Maintain normal body weight	5-10 for every 22lbs loss
Healthy eating plan	Meal plan rich in fruits, vegetables, low fat dairy and low in saturated fat and cholesterol	8-14
Sodium Restriction	Less than 2400 mg/day	2-8
Regular physical activity	30 min most days of the week	4-9

Hypertension and clotting disorders

- Treat hypertension to goal (<130/80 mmHg)
- Low dose diuretic
- ACE inhibitor (if also have DM)
- No particular agent is preferred for metabolc syndrome

Aspirin- to treat clotting disorders

Daily low dose aspirin (81-325mg) for men over age 45 and postmenopausal women

Metformins

- Metformin reduces blood glucose levels by inhibiting hepatic gluconeogenesis
  - Hepatic gluconeogenesis is active in patients due to liver's resistance to the effects of insulin
- Metformin also reduces lipid synthesis in the liver which aids in modulating blood lipid levels in these patients

Fibrates

- Used to reduce the lipid levels
- Target for fibrates is a transcription factor- peroxisome proliferator activated receptor-α
- PPAR- α when activated, leads to the transcription of genes involved in lipid degradation, or uptake by the cells. E.g.
  - Carnitine:palmitoyl transferase I- enhances the uptake of FA into the mitochondria
  - Lipoprotein Lipase
  - Stimulates apoAI and apoAII protein synthesis (major proteins in HDL)

THIAZOLIDINEDIONES (TZDS)

- Used for the treatment of insulin resistance and type 2 diabetes mellitus e.g. pioglitazone
- TZDs activate PPAR-γ class of transcription factors expressed primarily in the adipose tissue
- Activates the transcription of adiponectin
- The increase in adiponectin reduces the fat content of the liver and enhances insulin sensitivity

REFERNCES

- Lippincott