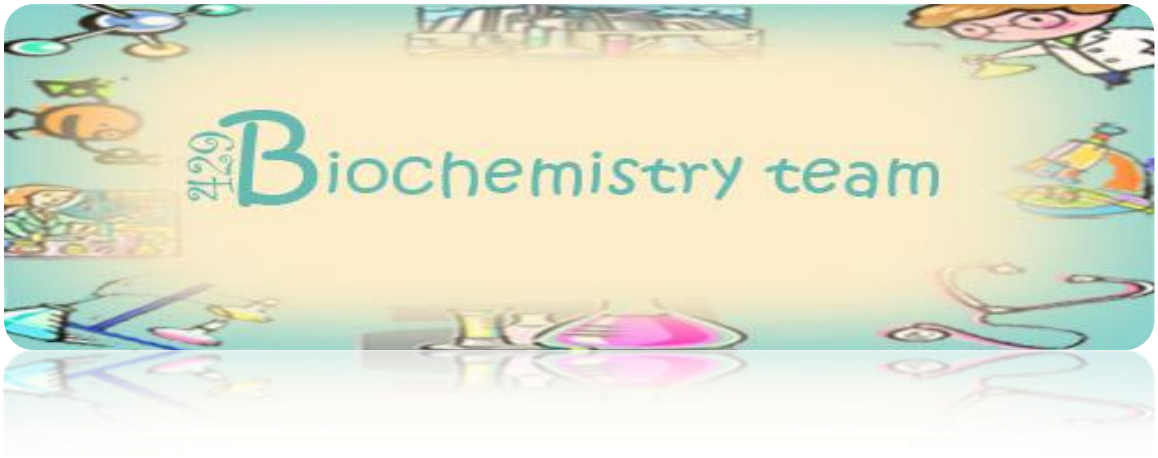

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Metabolic Syndrome

- A combination of metabolic abnormalities which increase the risk of heart disease, diabetes and other diseases
- Obesity is one of the causes of met. synd.
- Signals from adipocytes in obesity cause metabolic abnormalities such as:
  - Dyslipidemia
  - Glucose intolerance
  - Insulin resistance
  - Hypertension

Features of metabolic syndrome

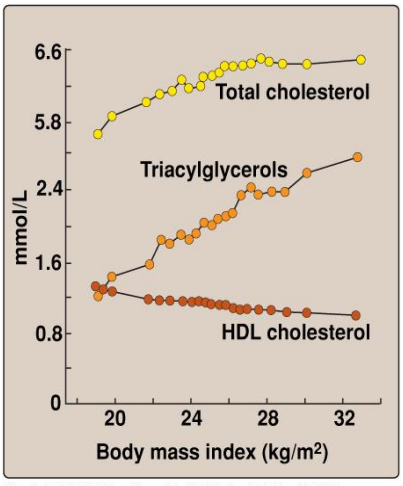
- Obesity
- High serum triglycerides (TGs)
- Low HDL cholesterol
- Hypertension
- Hyperglycemia
- Insulin resistance (hyperinsulinemia)

Insulin Resistance

- Cells become less responsive to insulin → high plasma insulin → hyperglycemia
- Hydrolysis of stored fats → high plasma FFAs
- Reduction of glucose uptake/use by cells
- Reduction of glycogenesis → hyperglycemia
- Compensatory hyperinsulinemia causes down regulation of insulin receptor
- Defects in insulin receptor

Dyslipidemia

- Insulin resistance in adipocytes → increased activity of hormone-sensitive lipase → high plasma FFAs
- FFAs → TGs/cholesterol in the liver
- Excess TGs/cholesterol are released as VLDL in the blood
- As a result, HDL levels are decreased



Dyslipidemia and met. synd. are strongly related

- Dyslipidemia is an early indicator of insulin resistance
- Liver fat plays a major role in dyslipidemia due to insulin resistance

Risk factors for metabolic syndrome

- Obesity
- Alcoholism
- Sedentary Lifestyle
- Smoking
- Hypercortisolism (Steroid use/Cushing's disease)
- Drugs (Rifampicin, isoniazid, etc.)
- Mutations in insulin receptor

- Everything contributing to obesity are contributing to inflammation
- smoking by itself cause inflammation b\c of ROS and other things→ contributing to metabolic syndrome

Metabolic syndrome is linked to:

- **Heart disease**
  - 1 .5-3 fold increase in atherosclerosis
- **Type-2 diabetes mellitus**
  - 5-fold increase
- **Kidney disease**
- **Reproductive abnormalities in women**
  - Polycystic ovarian syndrome
  - Impaired ovulation and fertility
  - Irregular menstruation
- **Nonalcoholic steatohepatitis (fatty liver disease)**
  - Related to impaired lipid metabolism
- **Cancer**
  - Obesity is a major risk factor for cancer of esophagus, colon and rectum, liver, gall bladder
  - 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
- Diabetes mellitus
- Insulin resistance
- PLUS any of these two:

- You don't have to remember the no.
- Impaired glucose tolerance = not able to utilize glucose (hyperglycemia)

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 General 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

- BP is not that high but along with other things it become risk factor
- Normal fasting glucose (70 – 100)
- In every criteria person should have glucose intolerance , if he doesn't have it but have dyslipidemia & HTN we call him (not metabolically healthy) .

NCEP* ATP** III Guideline (2002)

Diagnosis: **If any 3 or more 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 Program

**Adult Treatment Panel

Markers of metabolic syndrome

- Lipoproteins (LDL, HDL)
- Adipokines (Leptin, adiponectin)
- Inflammatory markers
  - c-reactive protein, TNF-a, IL-6, IL-8
- Hemostatic marker
  - Plasminogen Activator inhibitor-1

CRP= C reactive protein
Plasminogen Activator inhibitor-1→ inhibitor of fibrinolysis → clot formation →↑ risk of coronary heart disease , stroke , MI…etc !
These markers goes up in obesity and metabolic syndrome

Managing Metabolic Syndrome

- **Primary intervention**: Lifestyle changes
  - Weight reduction
    - Target BMI < 25
    - Reduced intake of calories and fats
    - More physical activity
  - Smoking cessation

- 1st thing to change is life style (don't start with medication)
- lifestyle change cause significant improvement
- we don't start from a very high goals otherwise the chance will failed

- **Secondary intervention**: 2ry Rx for the resistance risk factors
  Medication to treat existing risk factors
  - Management of
    - Blood pressure (anti-hypertensive drugs)
    - Lipids (statins, fibrates)
    - Blood glucose (metformin, TZDs)
  - Aspirin for CVD prevention

- Statins → for dyslipidemia
- Metformin → for diabetes
- Fibrates → for loweing cholecterol
- Thiazolidinediones (TZDs) → for glucose intolerance
- Aspirin therapy→ to remove the clotting !

Lowering blood pressure

If person reduces approximately 10 Kgs the systolic BP will drop at least 5 to 10

Modification	Recommendation	Average drop in SBP
Weight loss	Maintain normal body weight	5-10 for every 22lbs loss
Healthy eating plan	Meals rich in fruits, vegetables; low fat dairy; low saturated fats and cholesterol	8-14
Sodium restriction	< 2400 mg/day	2-8
Regular physical activity	30 min. most of the week	4-9

Hypertension and clotting disorders

- Treat hypertension to goal (< 130/80 mmHg)
- Low dose diuretics
- ACE inhibitor
- Aspirin:
  - To treat clotting disorders
  - Daily low dose aspirin (81-325mg) for:
    - Men > 45
    - Postmenopausal women

Some time diuretics has a side effect that ↑ impaired glucose tolerance
- ACE inhibitor = inhibit converging of angiotensin 1 to angiotensin 2

Current Treatment

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

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
- Reduces lipid synthesis in the liver
- Helps reducing blood lipids

Fibrates

- Reduce blood lipid levels
- Activate transcription factor:
  - Peroxisome proliferator activated receptor-α (PPAR-a)
- Activated PPAR- α → transcription of genes of lipid degradation / uptake by the cells:
  - Carnitine:palmitoyl transferase I (enhances FA uptake into mitochondria)
  - Lipoprotein Lipase
  - Stimulates apoAI and apoAII protein synthesis (major proteins in HDL)

- PPAR- α → transcription of genes
- When FFA was taken up by cells→ means removing from circulation .
- Fibrate ↑ HDL , ↓ FFA

Thiazolidinediones (TZDs) (Pioglitazone, rosiglitazone)

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

Remember !
PPAR- **α : Affect gene involved in lipolysis**
PPAR-**γ : Affect gene involved in adipose tissue**
Adiponectin inhibit gluconeogenesis & synthesis of FFA