

Metabolic Syndrome

Biochemistry Teamwork



Khalid Al-Khamis	Al-Anood Asiri
Abdulaziz Al-Shamlan	Lama Mokhlis
Abdullah Al-Mazyad	Noha Khalil
Turki Al-Otaibi	Reem Al-Mansour
Osamah Al-Jarallah	Nuha Al-Furayh
Saud Al-awad	Jumana Al-Shammari
Khaled Almohaimede	Deema Jomar
Meshal Al-Otaibi	Fatimah Abdulkarim
	Lamia Alghamdi

Done by: Reem Al-Mansour & Saud Al-awad

In green are notes.

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:

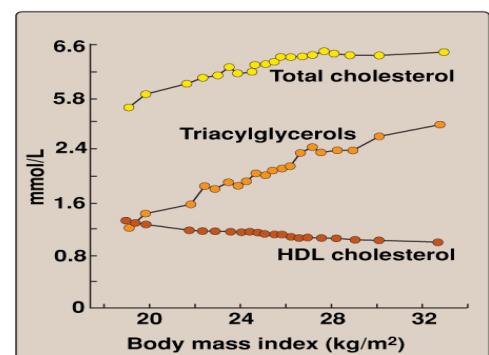
- A cluster of closely related medical conditions which increase the risk of developing heart disease and diabetes
- Features comprising Metabolic Syndrome
 - Obesity (specifically visceral)
 - High serum TGs
 - Low HDL cholesterol
 - Hypertension
 - Hyperglycemia
 - Hyperinsulinemia (insulin resistance)

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.



Copyright © 2002 Wolters Kluwer Health | Lippincott Williams & Wilkins

Dyslipidemia and the Metabolic Syndrome 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
- Hypercortisolism (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 and acne.

In PCOS the symptoms appears in the lady with or without the cysts in the ovaries.

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 General obesity	Waist to hip ratio >0.9 in men, >0.85 in women And/or BMI >30 * The BMI is taken sometimes with the waist to hip ratio and sometimes not.
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

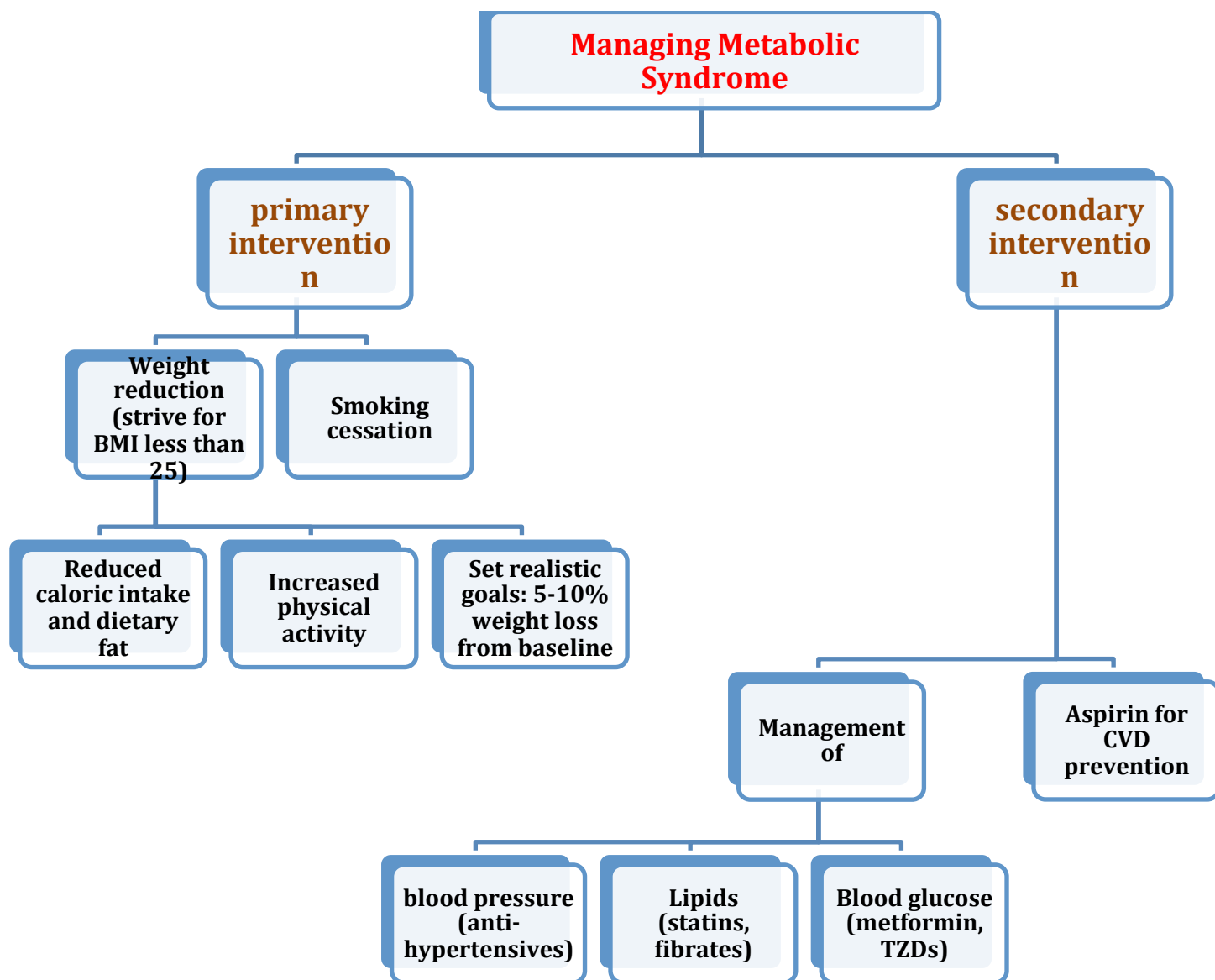
Markers of Metabolic Syndrome:

- Lipoproteins- LDL, HDL * the LDL becomes high and the HDL becomes low
- Adipokines-
 - Leptin
 - Adiponectin *will be low
- Inflammatory markers- CRP, TNF- α , IL-6, IL-8 *all will be high
- Hemostatic marker – Plasminogen Activator inhibitor-1

It is usually present in the endothelial cells but in the patients with metabolic syndrome they have thrombosis so this marker will be present in the circulation.

Current Treatments:

- Statins *for dyslipidemia
- Metformin *for diabetes
- Fibrates *for lowering blood lipid
- Thiazolidinediones (TZDs) *for blood sugar
- Aspirin therapy *prophylactic for coagulation



Primary intervention: (life style changes)

Secondary intervention: pharmacotherapy (for existing risk factors)

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 metabolic 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

Summary:

Metabolic syndrome is a combination of metabolic abnormalities which increase the risk of heart disease, diabetes and other diseases.

Obesity, high TGs, low HDL, hypertension, hyperglycemia, and insulin resistance are the features of metabolic syndrome.

High plasma FFAs causes insulin resistance.

In dyslipidemia, there is increased level of cholesterol and triacylglycerols and decreased level of HDL.

Risk factors for metabolic syndrome include: obesity, alcoholism, sedentary life style, smoking, hypercortisolism .

LDL, HDL, adipokines, inflammatory markers and hemostatic marker are the markers of metabolic syndrome.

In managing metabolic syndrome: primarily there is lifestyle changes like weight reduction and smoking cessation and secondarily some drugs which treat existing risk factors.

Questions:

- 1- which of the following is not a feature of metabolic syndrome :
 - A. Obesity.
 - B. Hypertension.
 - C. Hyperglycemia.
 - D. Fever.

- 2- which of these drugs can be a risk factor for metabolic syndrome :
 - A. Metformin.
 - B. Rifampicin.
 - C. Statins.
 - D. Fibrates.

Answers: D,B