

ENDOCRINE SYSTEM



LECTURE 2 :

METABOLIC SYNDROME

Objectives:

- 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

WHAT IS 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 TAGs
- Low HDL cholesterol
- Hypertension
- Hyperglycemia
- Hyperinsulinemia (insulin resistance) which will lead to the following:

Signals from adipocytes in obesity cause metabolic abnormalities such as:

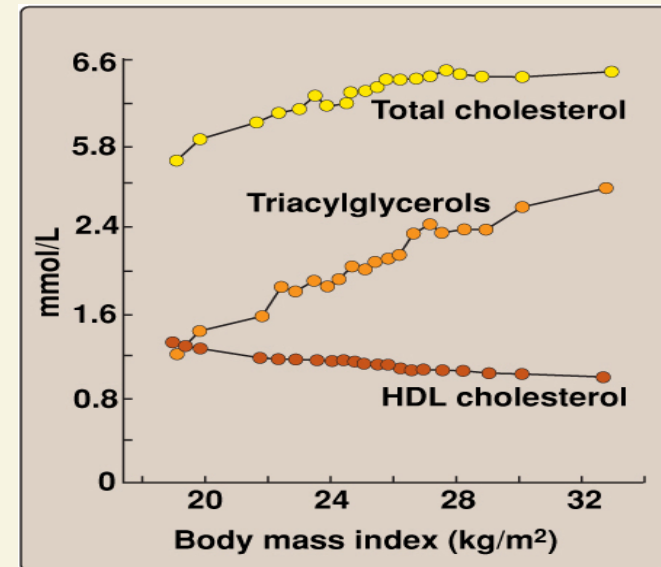
- Dyslipidemia
- Glucose intolerance
- Insulin resistance
- Hypertension

1. Reduction of glucose uptake (glucose utilization) among muscle cells because they become less responsive to insulin
2. Reduction of glycogenesis- (1 & 2 => lead to hyperglycemia)
3. Since the body is unable to utilize glucose for energy
=> Hydrolysis of stored TGs or fats will take place => leading to elevation of plasma FFA
4. Compensatory hyperinsulinemia causes down regulation of insulin receptors

INSULIN RESISTANCE AND DYSLIPIDEMIA

↑ production of insulin is an effort by the body to maintain blood glucose levels
This will cause increased activity of **hormone-sensitive lipase** (HSL), resulting in
=> ↑ levels of circulating fatty acids, which are carried to the **liver** and converted to **TGs and cholesterol**
=> Then they are released as **VLDLs**, resulting in elevated serum triacylglycerols
Concomitantly, **HDL levels are decreased**.

- ❑ Dyslipidemia and metabolic syndrome are strongly related
- ❑ 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)
- Mutation of insulin receptors

METABOLIC SYNDROME IS LINKED TO :

- Heart disease:
 - 1.5 - 3 fold increase for atherosclerotic
- Type 2 Diabetes Mellitus:
 - 5 fold increase
- Kidney disease
- Reproductive abnormalities in women:
 - Polycystic Ovarian Syndrome (PCOS)
 - Impaired ovulation and fertility
 - Irregular menstruations.
- Nonalcoholic steatohepatitis (fatty liver)
 - Related to distorted lipid metabolism
- Cancer
 - Obesity is major risk factor for cancer of the **esophagus, colon, rectum, liver, gall bladder**
 - Being overweight and obese accounts for 14% of all cancer deaths in men and 20% of those in women

DIAGNOSIS

According to the WHO criteria

- Impaired glucose tolerance
- DM
- insulin resistance

• PLUS at least two of the below mentioned components

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

According to the National Cholesterol Education Program and Adult Treatment Panel guidelines

Diagnosis: THREE OR MORE of these risk factors are present

Waist circumference	- Men >102 cm (>40 inch) - Women >88 cm (>35 inch)
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

DIAGNOSIS ,CONT'D (FOR READING)

Medscape®

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Risk factors	WHO [3]	NCEP ATP III [5,7]
	DM/IFG or IGT or IR plus at least two risk factors	Any ≥ 3 risk factors
Obesity	Waist-to-hip ratio >0.90 in men and >0.85 in women and/or BMI >30 kg/m ²	WC ≥ 102 cm in men or ≥ 88 cm in women
Triglycerides	≥ 150 mg/dl	≥ 150 mg/dl or drug treatment for elevated levels
HDL cholesterol	<35 mg/dl in men and <39 mg/dl in women	<40 mg/dl in men and <50 mg/dl in women or drug treatment for reduced levels
Blood pressure	$\geq 140/90$ mmHg	≥ 130 mmHg systolic or ≥ 85 mmHg diastolic or drug treatment for hypertension
Fasting plasma glucose	IGT, IFG, or type 2 DM	≥ 100 mg/dl or drug treatment for DM
Microalbuminuria	>30 mcg albumin/g creatinine	

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

Management of metabolic syndrome

Primary intervention

Lifestyle changes

Weight deduction

Smoking cessation

- Target BMI < 25
- ↓ Intake of calories and fats
- ↑ Physical activity

Secondary intervention

Medication to treat existing risk factors

Blood pressure & clotting disease

- Anti-hypertensive drugs
- Aspirin for CVD prevention

Dyslipidemia

- Statins
- Fibrates

Hyperglycemia

- Metformin
- TZDs

HYPERTENSION AND CLOTTING DISORDERS

LIFE STYLE MODIFICATIONS AND THEIR IMPACT ON LOWERING BP

Modification	Recommendation	Average drop in SBP (unit)
Weight loss	Maintain normal body weight	5-10 for every 22 lbs loss ¹
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

TREATING HYPERTENSION

The goal (< 130/80 mmHg)

- ✓ Low dose diuretics
- ✓ ACE inhibitor

TREATING CLOTTING DISEASE

Daily low dose aspirin (81-325mg) for:

- ◆ Men > 45
- ◆ Postmenopausal women

DYSLIPIDEMIA

STATINS & FIBRATES : BOTH REDUCE BLOOD LIPID LEVELS

MECHANISM OF ACTION OF FIBRATES :

- 1- Activate transcription factor called: Peroxisome proliferator activated receptor- α (PPAR- α)
- 2- Activated PPAR- α => \uparrow Transcription of genes of enzymes & proteins responsible for lipid degradation / uptake by the cells (such as) :
 - ✓ Carnitine:palmitoyl transferase I (enhances FA uptake into mitochondria)
 - ✓ Lipoprotein Lipase
 - ✓ Stimulates apoA1 and apoAII protein synthesis (major proteins in HDL)

HYPERGLYCEMIA

METFORMIN

EFFECT :

- ✓ Reduces blood glucose levels
- ✓ Reduces lipid synthesis in the liver¹

MECHANISM OF ACTION:

Inhibit hepatic gluconeogenesis²

- 1: Helps reducing lipid levels so, it has a dual action
- 2: Hepatic gluconeogenesis is active in patients with metabolic syndrome due to liver's resistance to the effects of insulin

THIAZOLIDINEDIONES (TZDS)

USES :

- Treat insulin resistance
- type-2 diabetes mellitus

MECHANISM OF ACTION:

A. TZDs activate PPAR- γ class of transcription factors (expressed primarily in the adipose tissue)

B. Activated PPAR- γ => Activate the transcription of adiponectin

=> **Adiponectin reduces the fat content of the liver and enhances insulin sensitivity**

Summary

- **Metabolic syndrome** is a cluster of closely related medical conditions which **increase the risk of developing heart disease and diabetes** and other diseases.
- **Risk factors for metabolic syndrome include:** **obesity**, alcoholism, **sedentary life style**, smoking, hypercortisolism .
- High plasma FFAs causes insulin resistance.
- **Markers of metabolic syndrome include:** LDL, HDL, adipokines, inflammatory markers and hemostatic marker .
- **Management of metabolic syndrome** : primarily there **is lifestyle changes** like weight reduction and smoking cessation and secondarily some drugs which treat existing risk factors.
- **Metformins:** reduces blood glucose levels and lipid synthesis.
- **Fibrates:** reduce the lipid levels, the target for fibrates is a transcription factor peroxisome proliferator activated receptor PPAR- α .
- **Thiazolidinediones (TZDs):** Used for the treatment of insulin resistance and type 2 diabetes mellitus e.g. pioglitazone, activate PPAR- γ .

TEST YOURSELF!

1- Which of the following is NOT an abnormality caused by obesity?

- a. Dyslipidemia
- b. High HDL
- c. Hypertension
- d. Diabetes mellitus

2. In metabolic syndrome, what is the main organ that plays a major role in causing dyslipidemia?

- a. Liver
- b. Kidney
- c. Waist adipocytes
- d. Breast adipocytes

3. Which of the following criteria fits to diagnose with metabolic syndrome Depending on WHO?

- a. DM + hypertension only
- b. DM + hypertension + high HDL
- c. DM + hypertension + low TGs
- d. DM + hypertension + microalbuminemia

4. In order to manage a cause of MS, hypertension & clotting disorder can be treated with?

- a. ACE agonists
- b. High dose of aspirin
- c. Low dose of diuretics
- d. Fibrates

5. Which of the following drugs inhibits gluconeogenesis?

- a. Metformin
- b. Fibrates
- c. Aspirin
- d. Statin

6. What is the mechanism of action for TZDs?

- a. Activates PPAR-alpha
- b. Activates PPAR-gamma
- c. In hepatocytes to increase excretion
- d. In duodenum to decrease the absorption

7. Which of the following is considered as marker for metabolic syndrome?

- a. Plasminogen (factor i clotting factor)
- b. Ghrelin
- c. LDL & HDL
- d. Creatine

8. Which of the following may occur in a female patient with metabolic syndrome?

- a. Malnutrition
- b. Anemia
- c. Polycystic ovarian syndrome
- d. Addison's disease

ANSWERS: 1.B 2.A 3.D 4.C 5.A 6.B 7.C 8.C

TEST YOURSELF!

Q9: A 45-year-old male presents concerned about his risk of developing diabetes. His family history reveals that his mother and maternal uncle are both diabetic.

He has central obesity with a waist measurement of 110 cm. On examination, his blood pressure (BP) is 130/82 mmHg, his body mass index (BMI) is 30.2 kg/m².

His investigations reveal:

Fasting cholesterol	5.2 mmol/l (<5.2)
Triglycerides	1.4 mmol/l (0.45-1.69)
HDL cholesterol	1.1 mmol/l (> 1.55)
Fasting glucose	6.2 mmol/l (3.0-6.0)

In addition to his waist measurement which of this man's observations fulfills the criteria for the diagnosis of the metabolic syndrome?

Which is the best answer?

- A) Blood pressure of 130/82 mmHg
- B) BMI of 30.2 kg/m²
- C) Fasting plasma glucose of 6.2 mmol/l
- D) HDL concentration of 1.1 mmol/l
- E) Triglyceride concentration of 1.4 mmol/l

10. As a pathophysiology of Dyslipidemia, excessive amount of triglycerides/cholesterol is released from the liver in the blood in form of?

- a. HDL
- b. VLDL
- c. Chylomicron
- d. Bilirubin

ANSWERS: 9. C 10. B

THANK YOU ...

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