



"اللَّهُمَّ لَا سَهْلَ إِلَّا مَا جَعَلْتَهُ سَهْلًا، وَأَنْتَ تَجْعَلُ الْحَزْنَ إِذَا شِئْتَ سَهْلًا"

# Metabolic syndrome

Color index:  
Doctors slides  
Doctor's notes  
Extra information  
Highlights



Endocrine block

# Objectives:

**By the end of this lecture, students should be able to:**

- Define metabolic syndrome, insulin resistance and dyslipidemia
- Discuss the risk factors for metabolic syndrome and other medical conditions associated with it
- Define the diagnostic criteria for Metabolic syndrome
- Discuss the management of metabolic syndrome and current treatment options

# Outline:

- Features of metabolic syndrome
- Insulin resistance
- Dyslipidemia
- Risk factors
- Markers
- Diagnosis
- Management and treatment

# Metabolic Syndrome

- A combination of metabolic abnormalities which increase the risk of heart disease, diabetes and other diseases
- Obesity is a component of met. synd.
- Signals from adipocytes in obesity cause metabolic abnormalities such as:
  - Dyslipidemia “↑LDL, ↑TG, ↓HDL”
  - Glucose intolerance
  - Insulin resistance
  - Hypertension

- Obesity is considered a low grade chronic inflammation that activates innate immunity.
- Adipocytes release inflammatory signals and contain immune cells

## Features of metabolic syndrome

- Obesity\*
- High serum triglycerides (TGs)
- Low HDL cholesterol
- Hypertension
- Hyperglycemia
- Insulin resistance (hyperinsulinemia) *the main issue*

Why do you think we have insulin resistance?  
This is a fighting mechanism as the body of an obese person is forcing him/her to use excess fat for energy instead of glucose .  
\*central obesity

It's not necessary that we found all of them

# Insulin Resistance

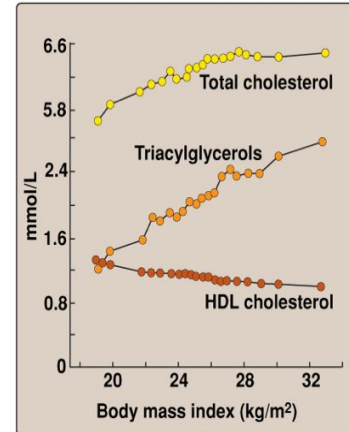
- Cells become less responsive to insulin → high plasma insulin → hyperglycemia
- Hydrolysis of stored fats → high plasma FFAs
- Reduction of glucose uptake/use by cells
- Reduction of glycogenesis → hyperglycemia
- Compensatory hyperinsulinemia causes down regulation of insulin receptor
- Defects in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

- Recall VLDL is a major carrier of TG's
- LDL/HDL major carrier of cholesterol.
- Why? Remember excess glucose gets converted in the liver into FFA +TG's + packaged into VLDL

## Dyslipidemia

- **Insulin resistance** = hyperinsulinemia 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
- HDL levels are decreased

\*which is involved in the process of lipolysis



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# Dyslipidemia and metabolic syndrome 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 of metabolic syndrome

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

### Why do we have dyslipidemia ?

- Insulin resistance (increase insulin) leads increase sensitivity to hormone sensitive lipase in adipocyte which breaks TG and release FFA
- Role of liver: insulin resistance leads to excess glucose in the blood which goes to the liver where it will get converted into FFA's and TG's and packaged in VLDL. In **normal people** there is an enzyme called lipoprotein lipase that will cleave VLDL and enter fat to cells and clear it from the blood. In **insulin resistance** the high levels of insulin in the blood will **inhibit** this enzyme and prevents fat clearance

# 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, gallbladder
  - 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

For diagnosis  
any one of  
these 3 + 2  
from table

PLUS any of these two:

*Know the numbers in table especially the first three  
also you should know the components*

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



# Diagnosis – NCEP ATP III Guideline (2002)

NCEP : National Cholesterol Education Program

ATP : Adult Treatment Panel

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



*You should also memorize these numbers*

# Markers of metabolic syndrome

- Lipoproteins (LDL is high, HDL is low)
- Adipokines (Leptin high or normal , adiponectin low)<sup>1</sup>
- Inflammatory markers <sup>2</sup>
  - c-reactive protein, TNF- $\alpha$ , IL-6, IL-8
- Hemostatic marker <sup>3</sup>
  - Plasminogen activator inhibitor-1

- 1 .recall that adiponectin level is parallel with HDL level ( here they are both low)
- 2.all inflammatory markers will be increased, because obesity is an inflammatory state
- 3.PAI-1: it inhibit fibrinolysis, in metabolic syndrome it increases so people are more prone to thrombosis
4. It is the first thing because obesity is the main component
5. Physical activity also increases your HDL levels (directly proportional)
6. Smoking is a risk factor for obesity and metabolic syndrome

# Managing metabolic syndrome

## 1- Primary intervention: Lifestyle changes

- Weight reduction <sup>4</sup>
  - Target BMI < 25
  - Reduced intake of calories and fats
  - More physical activity <sup>5</sup>
- Smoking cessation <sup>6</sup>

## 2- Secondary intervention: Medication to treat existing risk factors

- Management of
  - Blood pressure (anti-hypertensive drugs)
  - Lipids (statins, fibrates)
  - Blood glucose (metformin, TZDs)
- Aspirin for CVD prevention

# Lowering blood pressure



*You Dont need to memorize the numbers here*

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

This slide shows how blood pressure is affected by lifestyle modification ( average drop in systolic blood pressure that can be achieved by doing this modification)


\*SBP= systolic blood pressure

# Hypertension and clotting disorders

- Treat hypertension to goal (< 130/80 mmHg)
- Low dose diuretics
- ACE inhibitor <sup>1</sup>
- Aspirin:
  - To treat clotting disorders
  - Daily low dose aspirin (81-325mg) for:
    - Men > 45
    - Postmenopausal women

## Current Treatment

- Statins <sup>2</sup>
- Metformin <sup>3</sup>
- Fibrates
- Thiazolidinediones (TZDs)
- Aspirin



*Dr said : what I need u to know the Biochemical effect of these drugs.*

1. ACEI is preferred in diabetes because it protects from diabetic nephropathy

2. Are used to treat hyperlipidemia. They work by blocking HMG-CoA reductase ( a key enzyme in the synthesis of cholesterol) , it reduces LDL level

3. Anti diabetic drug

# 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 <sup>1</sup>:
  - Peroxisome proliferator activated receptor- $\alpha$  (PPAR- $\alpha$ )
- Activated PPAR- $\alpha$   $\rightarrow$  transcription of genes of lipid degradation / uptake by the cells:
  - Carnitine: **palmitoyl transferase I** (enhances FA uptake into mitochondria)
  - Lipoprotein Lipase “enhances TG uptake into the cell”
  - Stimulates **apoAI** and **apoAII** protein synthesis (major proteins in HDL) <sup>2</sup>

1.transcription factors are certain molecules that binds to regions in the DNA before the gene, and they affect the transcription of that gene, either increase transcription or decrease it ( usually increase)

2. Increase the amount of HDL, correct the dyslipidemia

# Thiazolidinediones (TZDs)

- Used for the treatment of insulin resistance and type-2 diabetes mellitus
- TZDs activate PPAR-g (*gamma*) 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

- Metabolic Syndrome : A combination of metabolic abnormalities which increase the risk of heart disease, diabetes and other diseases
- Signals from adipocytes in obesity cause metabolic abnormalities such as :
  - Dyslipidemia : increase VLDL in the blood , HDL levels are decreased  
Dyslipidemia is an early indicator of insulin resistance
  - Glucose intolerance
  - Insulin resistance
  - Hypertension
- Metabolic syndrome is linked to : 1-Nonalcoholic steatohepatitis 2-Cancer

## Diagnosis

### 1-WHO criteria :

- Impaired glucose tolerance
  - Diabetes mellitus
  - Insulin resistance
- PLUS any of these two:
- Hypertension
  - Dyslipidemia
  - Central or General obesity
  - Microalbuminuria

### 2-NCEP ATP III Guideline :

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
- Bloodpressure 130/ 85 mmHg
- Fasting glucose >100 mg/dL

## Managing Metabolic Syndrome

• Primary intervention:	Lifestyle changes	
• Secondary intervention	Medication to treat existing risk factors like hypertension	
• Current Treatment	1-Metformin	-inhibit hepatic gluconeogenesis -Reduces lipid synthesis in the liver
	2-Fibrates	-Reduce blood lipid levels -Activate (PPAR- $\alpha$ ) $\rightarrow$ lipid degradation / uptake by the cells
	3-Thiazolidinediones	-Used for the treatment of insulin resistance and type-2 diabetes mellitus -activate PPAR- $\gamma$ $\rightarrow$ Activates the transcription of adiponectin $\rightarrow$ Adiponectin reduces the fat content of the liver and enhances insulin sensitivity



# Take Home Messages

- Metabolic syndrome is a combination of metabolic abnormalities that increase the risk of heart disease, diabetes and other diseases
- The features of metabolic syndrome include obesity, high serum triglycerides (TGs), low HDL cholesterol, hypertension, hyperglycemia and insulin resistance
- Obesity, alcoholism, sedentary lifestyle and smoking are some of the risk factors for metabolic syndrome
- Management of the syndrome includes lifestyle modifications to reduce weight and medications

# MCQs:

**Q1 : Which one of the following is correct in metabolic syndrome?**

- A. High Serum TGs
- B. High HDL
- C. Hypoglycemia
- D. Glucose tolerance

**Q2 : Which one of the following is correct about insulin resistance?**

- A. Cells have an increased response to insulin
- B. High plasma FFA
- C. Low plasma Insulin
- D. Hypoglycemia

**Q3 : Which one of the following is a marker for metabolic syndrome?**

- A. Low LDL
- B. increase Adiponectin
- C. High IL-6
- D. Decreased Leptin

**Q4 : Which one of the following is a good management plan for hypertension?**

- A. glucagon
- B. Aspirin
- C. Statins
- D. Metformin

## Girls team

- لجين عبدالله
- مشاعل القحطاني
- رزان الزهراني

## Boys team

- معن شكر
- نواف اللويحي
- انس القحطاني
- نايف المطيري
- طارق العميم

## Team leaders

- رهام الحلبي
- معاذ الحمود



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