Metabolic Syndrome

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Color Index:

- **Main Topic**
- **Main content**
- **Important**
- **Drs' notes**
- **Extra info**

Editing File

Objectives:

- 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
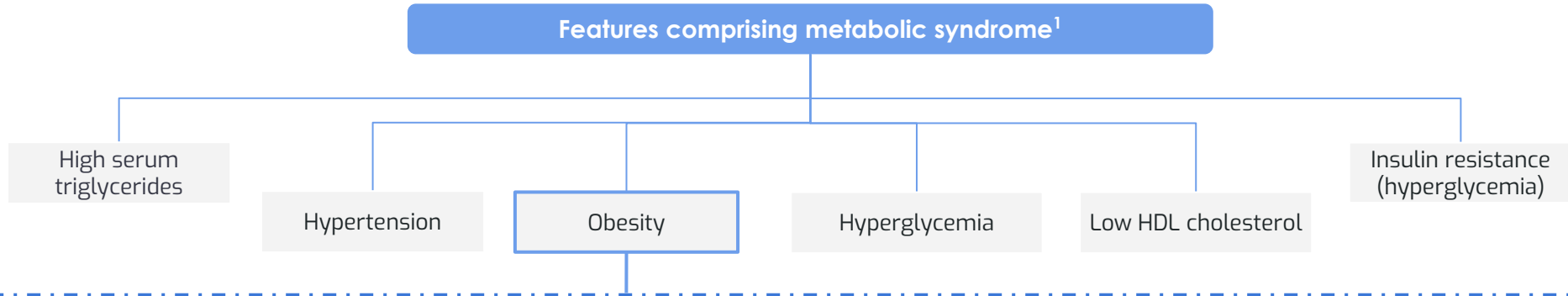- Discuss the management of metabolic syndrome and current treatment options

Overview:

- Introduction
- Features of metabolic syndrome
- Insulin resistance
- Dyslipidemia
- Risk factors
- Markers & diagnosis
- Management & treatment

Metabolic Syndrome

It is a combination of metabolic abnormalities which increase the risk of **heart disease**, **diabetes**, & other diseases

Features comprising metabolic syndrome[1]

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

- In obesity, signals from adipocytes cause metabolic abnormalities such as:

  - Dyslipidemia *(next slide)*
  - Insulin resistance [2]
  - Glucose intolerance
  - Hypertension

  - 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 → **down-regulation** of insulin receptors
  - Defects in insulin receptor

1- NOTE from 437: not necessary to find them all
2-NOTE from 437: 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

Dyslipidemia

Insulin resistance in adipocytes (in obese individuals)	increased activity of hormone sensitive lipase[1]	High plasma FFAs ⇒ get carried to the liver & converted to: TG/cholesterol in the liver	Excess TGs/ cholesterol are released as VLDL[2] to the blood	HDL levels are decreased

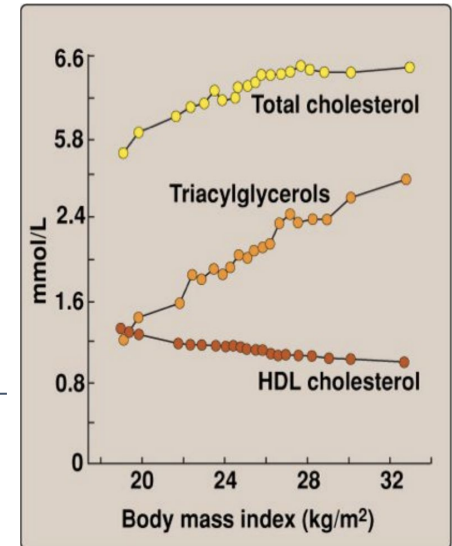## Metabolic syndrome & dyslipidemia are closely related:

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

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1) increased activity of lipase is because body can not use glucose as source of energy , the other source is FFAs which are broken down from triglycerides in adipocytes.

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

Metabolic Syndrome Is Related 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 & fertility, irregular menstruation

Nonalcoholic steatohepatitis (fatty liver disease)

Related to impaired lipid metabolism

Cancer
- Obesity is a major risk factor for cancer of the esophagus, colon & rectum, liver, gallbladder
- Being overweight and obese accounts for 14% of all cancer deaths in men and 20% of those in women

Risk factors for Metabolic Syndrome

Smoking/alcoholism

Obesity

Sedentary lifestyle

Drugs (Rifampicin, Isoniazid, etc)

Hypercortisolism (Steroid use/ Cushing disease)

Mutations of insulin receptor

Diagnosis				Markers	
WHO criteria (1999)		**NCEP* ATP** III Guideline (2002)**		**Lipoproteins**	HDL (low) LDL (high)
One of the following: impaired glucose tolerance / diabetes mellitus / insulin resistance **plus any 2 from what is mentioned below**		If any 3 or more of these risk factors are present		**Adipokines**	-Leptin (high or normal) -Adiponectin (parallel with HDL levels, so low)
Hypertension	BP >140/90 mmHg	**Blood pressure**	130/ 85 mm Hg	**Inflammatory markers** (obesity is an inflammatory state)	- C reactive protein - TNF a - IL - 6 - IL - 8 (All will be high)
Dyslipidemia	• High plasma TGs (>1.7mmol/L) • Low HDL cholesterol (men <0.9, women <1.0 mmol/L)	**Triglycerides**	>150 mg/dL		
Central or General obesity	• Waist to hip ratio >0.9 in men, >0.85 in women • And/or BMI >30	**HDL cholesterol**	• Men<40 mg/dL • Women<50 mg/dL	**Hemostatic marker**	Plasminogen activator inhibitor - 1 (PAI 1) PAI 1 inhibits fibrinolysis. Therefore, in metabolic syndrome people will be more prone to thrombosis
Micro-albuminuria	Urinary albumin excretion rate ≥ 20ug/min; or albumin:creatinine ratio ≥ 30mg/g	**Waist circumference**	• Men>102 cm (>40 in) • Women>88 cm (>35 in)		
		Fasting glucose	>100 mg/dL		

Managing Metabolic Syndrome

Primary intervention: Lifestyle changes
- weight reduction [1]
- Target BMI < 25
- Reduced intake of calories and fats
- More physical activity [2]
- Smoking cessation [3]

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

Modification	Recommendation	Average drop in SBP*
Weight loss	Maintain normal body weight	5-10 for every 22lbs
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

1.It is the first thing because obesity is the main component
2. Physical activity also increases your HDL levels (directly proportional)
3. Smoking is a risk factor for obesity and metabolic syndrome

You don't have to memorize the numbers here
This table 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

1 — Treat hypertension to goal (< 130/80 mmHg)

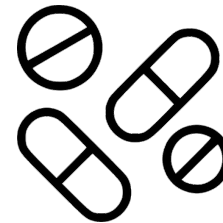**3** — ACE inhibitor [1]

2 — Low dose diuretics

4 — Aspirin:

- To treat **clotting** disorders
- Daily low dose aspirin (81 - 325 mg) for:
- Men > 45
- Postmenopausal women

Current treatment

- Statins [2]
- Metformin [3]
- 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, fibrates, TZDs

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

436 notes :
-If we give metformin to obese person who doesn't have diabetes, it can lower body weight by decreasing lipid synthesis and blood glucose.
-When there's **insulin resistance** (the cell can't take up the glucose) the body perceives starving mode and the liver starts **gluconeogenesis** to make glucose which is a way to get **hyperglycemia**.

Fibrates

● Reduce blood lipid levels

● Activate transcription factor[1]:

○ Peroxisome proliferator activated receptor-a (**PPAR-a**)

● Activated PPAR-a → 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)[2]

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

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

Take Home Messages

Metabolic syndrome is a combination of metabolic abnormalities that increase the risk of heart disease, diabetes and other diseases
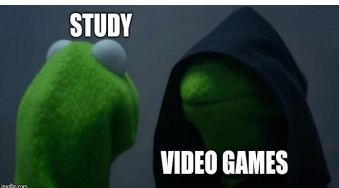
The features of metabolic syndrome include obesity, high serum triglycerides (TGs), low HDL cholesterol, hypertension, hyperglycemia and insulin resistance

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

Summary

Metabolic Syndrome	it is a combination of metabolic abnormalities which increase the risk of heart disease, diabetes and other diseases.
Features of metabolic syndrome	1-Hyperglycemia 2-Hyperinuslinemia 3-Low HDL cholesterol 4-Obesity 5-Hypertension 6-High serum Triglyceride
Risk factors for metabolic Syndrome:	1-Obesity 2-Alcohol 3-Drugs (Isoniazied, Rifampicin) 4-Sedentry lifestyle 5-High cortisol level 6-Mutation in insulin receptor
Metabolic Syndrome is linked to:	1-Heart disease 2-Kidney disease 3-Cancer 4-DMT2 5-Non alcoholic steatohepatitis
Metabolic syndrome markers	Lipoproteins (HDL, VLDL), Adipokines (Leptin, Adiponectin), Inflammatory markers and haemostatic markers
Managing metabolic syndrome:	Life style medication
WHO Citeria	One of the following: • Impaired glucose tolerance, Diabetes mellitus and Insulin resistance • PLUS two of the following: • Hypertension, dyslepedima, microalbumenia, obesity
NCEP ATP III Guideline (2002)	If any 3 or more of the following risk factors are present: ✓ Waist circumference: ✓ Triglycerides ✓ HDL cholesterol ✓ Blood pressure ✓ Fasting glucose

Quiz

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 a marker for metabolic syndrome?
a) Low LDL   **b)** increase Adiponectin   **c)** High IL-6   **d)** Decreased Leptin

Q3: Which one of the following is a good management plan for hypertension?
a) ACE inhibitors   **b)** Aspirin   **c)** Statins   **d)** Metformin

Q4: 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

Q5: Which of the following criteria fits to diagnose metabolic syndrome depending on the WHO?
a) DM + hypertension only   **b)** DM, hypertension, & dyslipidemia
c) DM + dyslipidemia   **d)** hypertension + low TGs

Q6: According to WHO criteria to diagnose MS the blood pressure must be:
a) >140/90 mmHg   **b)** 135/85 mmHg
c) 130/85 mmHg   **d)** < 140/90 mmHg

SAQs :

Q1: Mention 3 abnormalities caused by obesity?

Q2: List 4 features that comprise the metabolic syndrome?

Q3: List 3 risk factors of metabolic syndrome.

Q4: list the markers for MS.

★ **MCQs Answer key:**

1) A   2) C   3 A   4) B   5) B   6) A

★ **SAQs Answer key:**

1) Dyslipidemia, hypertension, insulin intolerance

2) Obesity, hypertension, insulin resistance, low HDL cholesterol

3) Obesity, smoking, alcoholism.

4) Slide 6

Team members

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★ **Life is a succession of lessons which must be lived to be understood.**

438 BIOCHEMISTRY TEAM

We hear you

13