Revised & Approved

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BIOCHEMISTRY TEAM
439

MED439
KING SAUD UNIVERSITY

Metabolic syndrome

Editing File

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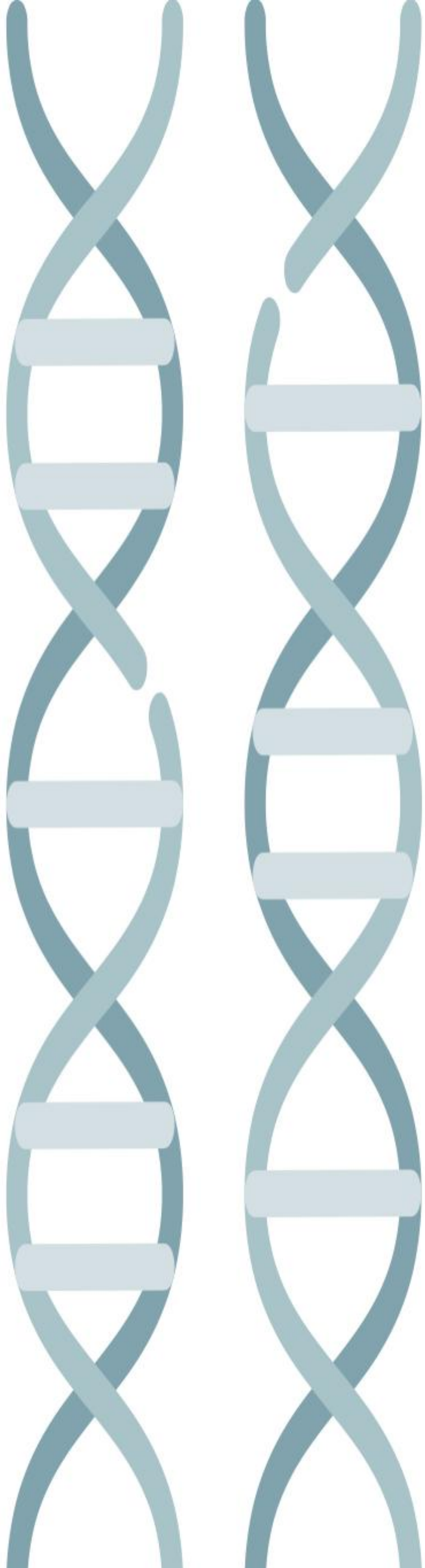
- Main Text
- Important
- Extra
- Dr.'s Notes
- Girls slides
- Boys slides

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

- High serum triglycerides
- Hypertension
- **Obesity** — It's chronic low-grade inflammation
- Hyperglycemia
- Low HDL cholesterol
- Insulin resistance (hyperglycemia)

In obesity, signals from adipocytes (adipokines) most of them are pro-inflammatory cause metabolic abnormalities such as:

- Dyslipidemia
- Insulin resistance
- Glucose intolerance
- Hypertension

Initiating events: Genetics predisposition and Obesity (adipokines)

- Cells become less responsive to insulin → high plasma insulin → hyperglycemia
  As a compensatory mechanism that will succeed at first but after few years will develop DM
  -Hydrolysis of stored fats as result of starvation → high plasma FFAs and glycerol
  -Reduction of glucose uptake/use by cells
  -Reduction of glycogenesis → hyperglycemia (Starvation-like condition) inhibit the liver enzymes involved in glycogenesis
- Compensatory hyperinsulinemia → down-regulation of insulin receptors (because it will exposed to high level of insulin)
- Defects in insulin receptor

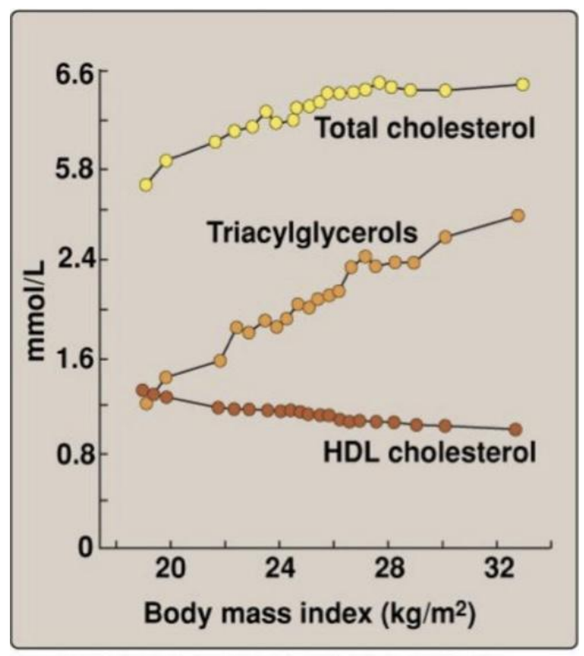
And ↓Lipoprotein lipase in capillary wall near the adipocytes

- ↓ Breakdown of TAG into VLDL (endogenous TAG) and chylomicrons (dietary TAG) and facilitating its uptake

Insulin resistance in adipocytes (in obese independent) → Increased activity of hormone sensitive lipase → High plasma FFAs ⇒ get carried to the liver & converted to: TG/cholesterol in the liver → Excess TGs/ cholesterol are released as VLDL 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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Metabolic Syndrome Is Related to

Heart disease
1.5-3 fold increase in atherosclerosis

Type 2 diabetes mellitus
5 fold increase

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.

Kidney disease

Nonalcoholic steatohepatitis (fatty liver disease)
Related to impaired lipid metabolism

Fat accumulation in the liver will lead to inflammation

Reproductive abnormalities in women
Polycystic ovarian syndrome, impaired ovulation & fertility, irregular menstruation

Risk factors for Metabolic Syndrome

- Smoking/alcoholism
  - Smoking = ↑inflammation
  - Alcoholism = severe alcohol abuse
- Obesity
- Sedentary lifestyle
- Drugs (Rifampicin, Isoniazid, etc)
- Hypercortisolism (Steroid use/ Cushing disease)
- Mutations of insulin receptor

Diagnosis (Imp) numbers are not important

WHO criteria (1999)		NCEP* ATP** III Guideline (2002)	
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	
Hypertension	BP >140/90 mmHg	**Blood pressure**	130/ 85 mm Hg
Dyslipidemia	• High plasma TGs (>1.7mmol/L) • Low HDL cholesterol (men <0.9, women <1.0 mmol/L)	**Triglycerides**	> 150 mg/dl
Central (W:H ratio) and mostly will contribute in metabolic syndrome **or General obesity** (BMI)	• Waist to hip ratio >0.9 in men, >0.85 in women HDL • And/or BMI >30	**HDL Cholesterol**	• Men<40 mg/dL • Women<50 mg/dL
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

Markers of Metabolic syndrome (Imp)		
	Lipoproteins	HDL (low) LDL (high)
	Adipokines	• Leptin (high or normal) • Adiponectin (parallel with HDL levels, so low)
	Inflammatory markers (obesity is an inflammatory state)	• C reactive protein • TNF-a secreted by macrophages inside adipocytes & smooth muscle cells causing phosphorylation and inactivation of insulin receptors and interfering with adiponectin release • IL - 6 secreted by adipocytes & Immune cells causing ↑ Fibrinogen level (prothrombotic state) • IL - 8 (All will be high)
	Hemostatic Marker	Plasminogen activator inhibitor - 1 (PAI 1) PAI 1 inhibits fibrinolysis. Therefore, in metabolic syndrome people will be more prone to thrombosis Mainly produced by endothelium but also by adipocytes causing Fibrinolysis

Managing Metabolic Syndrome
(Dual approach)

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

Secondary intervention (if primary intervention not help only) : 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 numbers are not important

(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)

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

Hypertension and Clotting Disorders

Treat hypertension to goal (< 130/80 mmHg)

Low dose diuretics

ACE inhibitor
Drug of choice for DM because it's protective against diabetic nephropathy

Aspirin produces TXA2 which prevents platelets aggression
-To treat clotting disorders
-Daily low dose aspirin (81 - 325 mg) for: (protective therapy)
- Men > 45
- Postmenopausal women

Current treatment

- Statins inhibit HMG-CoA reductase which is the key enzyme for cholesterol biosynthesis resulting in ↓ LDL
- Metformin first-line glucose-lowering agent in patients with type 2 diabetes
- Fibrates
- Thiazolidinediones (TZDs)
- Aspirin

1.ACEI is preferred in diabetes because it protects from diabetic nephropathy - Aspirin
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 Dr said : what I need u to know the Biochemical effect of these drugs.
3. Anti diabetic drug

Metformin	Fibrates	Thiazolidinediones(TZDs)
Reduces blood glucose levels 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 content of the liver and enhances decreasing lipid synthesis and blood glucose. insulin sensitivity -When there's **insulin resistance** (the cell can't take synthesis (major proteins in HDL)2 up the glucose) the body perceives starving mode and the liver starts **gluconeogenesis** to make glucose which is a way to get **hyperglycemia**.	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 will clear plasma lipoproteins "enhances TG uptake into the cell" in case of Insulin resistance • Stimulates **apoAI** and **apoAII** protein synthesis (major proteins in HDL) • **apoAI** and **apoAII increase amount of HDL**	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** the good adipokine! • Adiponectin reduces the content of the liver and enhances insulin sensitivity facilitate the glucose uptake by the cells = ↓blood glucose level

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	a combination of metabolic abnormalities which increase the risk of heart disease, diabetes, & other diseases
Features of metabolic syndrome	• Hyperglycemia • Hyperinsulinrmia • Low HDL cholesterol • Obesity • Hypertension • High serum triglyceride
Risk factors for metabolic syndrome	• Obesity • Alcohol • Drugs (isoniazid, Rifampicin) • Sedentary lifestyle • High cortisol level • Mutation in insulin reseptor
Metabolic syndrome is linked to:	• Heart disease • Kidney disease • Cancer • DMT2 • Non alcoholic steatohepatitis
Metabolic syndrome markers	• Lipoproteins (HDL, VLDL) • Adipokines (Leptin, Adiponectin) • Inflammatory markers • Haemostatic markers
Managing metabolic syndrome:	• Lifestyle • Medication
WHO criteria	<u>One</u> of the following : • Impaired glucose tolerance • Diabetes mellitus • Insulin resistance <u>Plus</u> two of the following : • Hypertension • Dyslipidemia • Microalbuminuria • 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

MCQs

1- Which one of the following is correct in metabolic syndrome?			
A-High Serum TGs	B-High HDL	C-Hypoglycemia	D-Glucose tolerance
2- Which one of the following is a marker for metabolic syndrome?			
A-Low LDL	B-increase Adiponectin	C- High IL-6	D-Decreased Leptin
3-Which one of the following is a good management plan for hypertension?			
A-ACE inhibitors	B- Aspirin	C-Statins	D-Metformin
4-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
5- 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
6-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

Answers key

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

SAQs

1- List 4 features that comprise the metabolic syndrome?

Obesity, hypertension, insulin resistance, low HDL cholesterol

2- List 3 risk factors of metabolic syndrome.

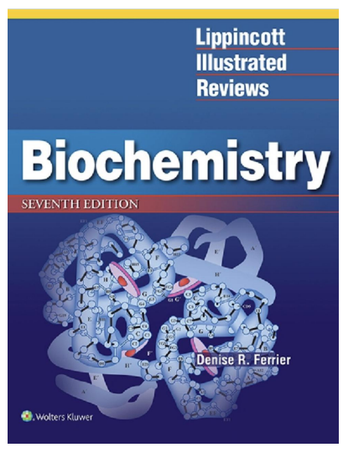
Obesity, smoking, alcoholism.

3- Mention 3 abnormalities caused by obesity?

Dyslipidemia, hypertension, insulin intolerance

Resources

Click on the book to download the resource



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