

L10: Metabolic syndrome

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Main Text

Male's Slides

Female's Slides

Important

Doctor's Notes

Extra Info

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Objectives

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

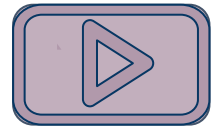
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Biochemistry 443 team channel: 

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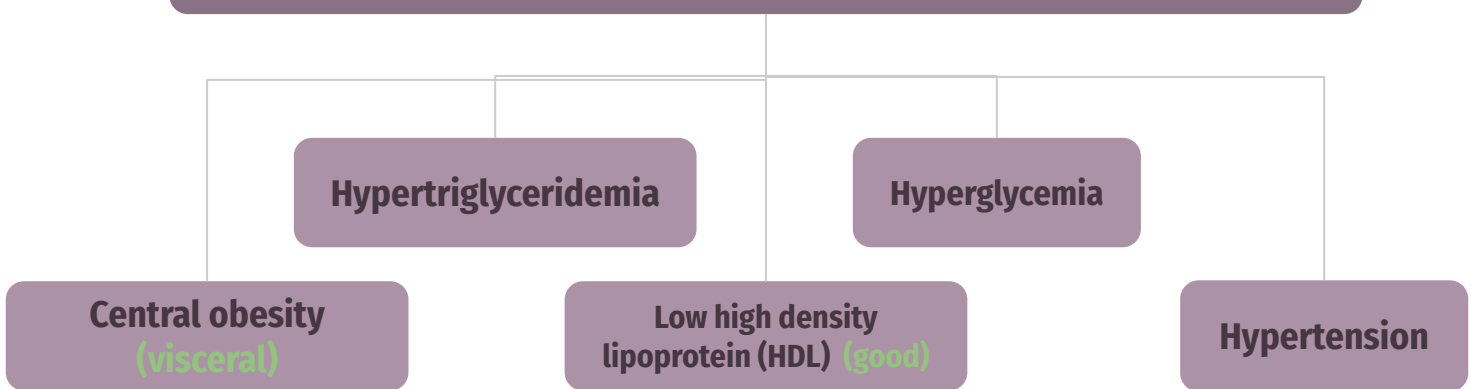
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Metabolic Syndrome

It is a constellation of metabolic abnormalities that confer increased risk of cardiovascular disease (CVD), diabetes mellitus.

Major Features of Metabolic Syndrome



Metabolic Syndrome is Linked To:

01

Heart Disease

1.5-3 fold increase in atherosclerosis

02

Type 2 Diabetes

5-fold increase

03

Kidney Disease

04

Reproductive Abnormalities in Women

- Polycystic ovarian syndrome
- Impaired ovulation & fertility
- Irregular menstruation

05

Non-alcoholic steatohepatitis (fatty liver disease)

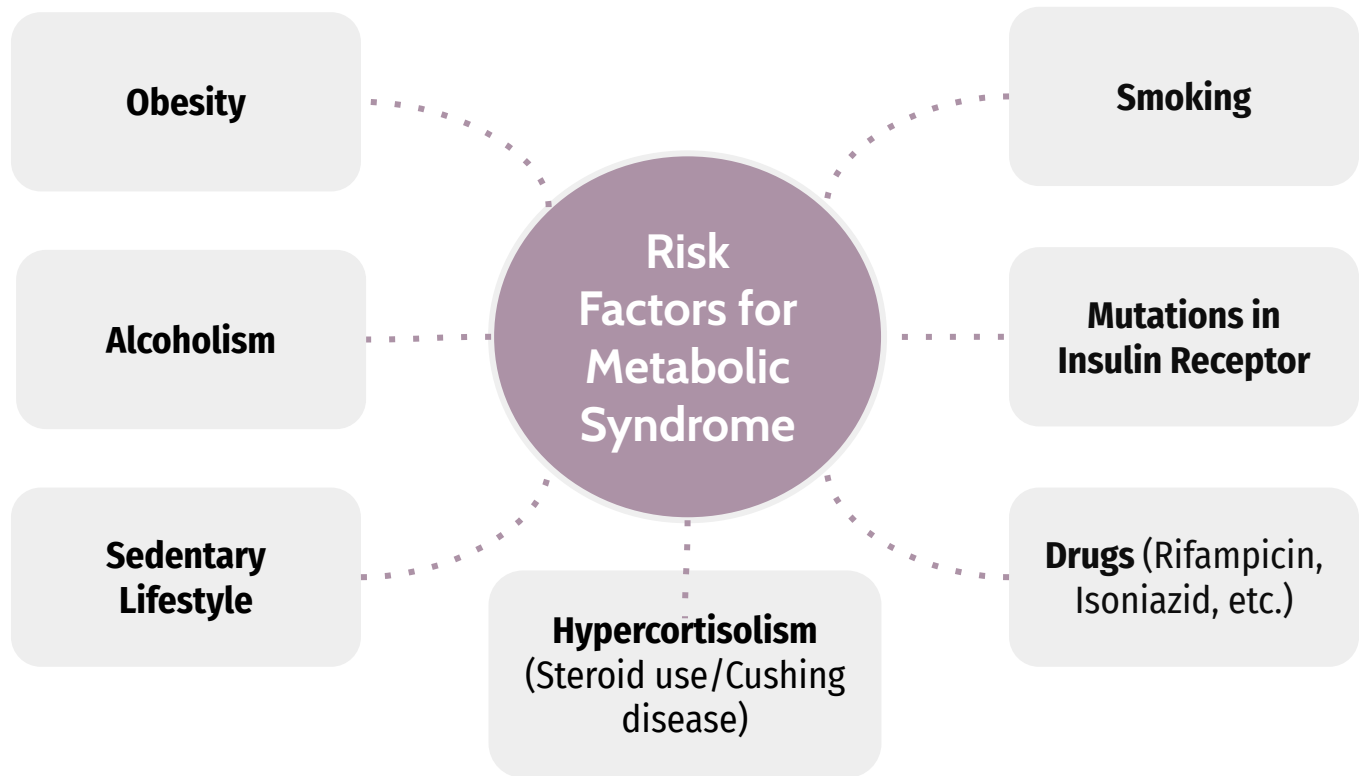
Related to impaired lipid metabolism

06

Cancer

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

Metabolic Syndrome



Diagnosis

WHO Criteria (1999)		NCEP* ATP** Guideline (2002) + Consensus definition [^]	
Impaired glucose tolerance or diabetes mellitus or insulin resistance plus any of the 2 below:		If any 3 or more of these risk factors are present:	
Hypertension	BP > 140/90 mmHg	Blood Pressure	130/85 mmHg
Dyslipidemia	<ul style="list-style-type: none"> ↑ plasma TGs (>1.7mmol/L) ↓ HDL cholesterol (men <0.9, women <1.0 mmol/L) 	Triglycerides	> 150 mg/dl
		HDL Cholesterol	<ul style="list-style-type: none"> Men <40 mg/dL Women <50 mg/dL
Central or General Obesity	<ul style="list-style-type: none"> Waist to hip ratio >0.9 in men, >0.85 in women And/or BMI >30 	Waist Circumference	<ul style="list-style-type: none"> Men >102 cm (>40 in) Women >88 cm (>35 in)
Microalbuminuria	<ul style="list-style-type: none"> Urinary albumin excretion rate ≥ 20µg/min Or albumin:creatinine ratio ≥ 30 mg/g 	Fasting Glucose	> 100 mg/dL

[^]Waist circumference in Consensus definition is Population & country specific, others are the same as 2002

* NCEP: National Cholesterol Education Program

**ATP: Adult Treatment Panel

Consensus Definition - 2009

Table 1. Definitions of metabolic syndrome.

Clinical measure	World Health Organization 1998 ⁷	European Group for the Study of Insulin Resistance 1999 ⁸	Adult Treatment Panel III of the National Cholesterol Education Program 2001 ¹⁰	International Diabetes Federation 2005 ¹¹	American Heart Association/National Heart, Lung, and Blood Institute 2005 ¹²
Criteria	IR + any other 2	IR + any other 2	Any 3 of 5	Increased WC (population specific) + any other 2	Any 3 of 5
Insulin resistance	IGT/IFG IR	Plasma insulin > 75th percentile	-	-	-
Blood glucose	IFG/IGT/T2DM	IFG/IGT (excludes diabetes)	≥ 110 mg/dL (includes diabetes)	≥ 100 mg/dL	≥ 100 mg/dL (includes diabetes)
Dyslipidemia	TG ≥ 1.69 mmol/L and HDL-C men < 0.90 mmol/L women < 1.01 mmol/L	TG ≥ 1.69 mmol/L and HDL-C < 1.01 mmol/L in men and women	TG ≥ 1.69 mmol/L HDL-C men < 1.03 mmol/L women < 1.29 mmol/L	TG ≥ 1.69 mmol/L or on TG treatment HDL-C men < 1.03 mmol/L women < 1.29 mmol/L Or HDL treatment	TG ≥ 1.69 mmol/L or on TG treatment HDL-C men < 1.03 mmol/L women < 1.29 mmol/L Or HDL treatment
Blood pressure	≥ 140/90 mmHg All others are waist circumference	≥ 140/90 mmHg or on antihypertensive medications	≥ 130/85 mmHg or on antihypertensive medications	≥ 130/85 mmHg or on antihypertensive medications	≥ 130/85 mmHg or on antihypertensive medications
Obesity	Waist: hip ratio men > 0.9 women > 0.85 and/or BMI > 30 kg/m ²	WC men ≥ 94 cm women ≥ 80 cm	WC men ≥ 102 cm women ≥ 88 cm	WC ≥ 94 cm	WC men ≥ 102 cm women ≥ 88 cm
Other	Microalbuminuria → Involvement of kidney				

BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; IR, insulin resistance; T2DM, type 2 diabetes mellitus; TG, triglycerides; WC, waist circumference. (Adapted from the American Heart Association/National Heart, Lung, and Blood Institute report.¹³)

Consensus Definition

In 2009, a harmonized consensus definition was agreed by the International Diabetes Federation; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity

Any 3 of the following criteria:

***Know numbers**

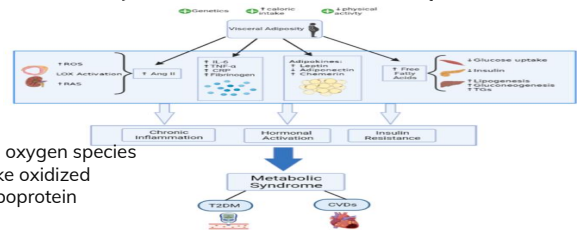
Measure	Cut Points
Elevated waist circumference	Population & country-specific
Elevated Triglycerides (or on therapy for hypertriglyceridemia)	≥ 150 mg/dL
Reduced HDL-C (or on therapy for reduced HDL-C)	< 40 mg/dL in males < 50 mg/dL in females
Elevated blood pressure (or on therapy with known history of HTN)	SBP ≥ 130 and/or DBP ≥ 85 mmHg
Elevated fasting glucose (or on therapy for hyperglycemia)	≥ 100 mg/dL

Notice that **blood insulin is not part of the five criteria** because measuring this parameter for large-scale screening is cumbersome in clinical practice.

Pathophysiology

- Visceral adiposity → activates most of the pathways of metabolic syndrome.
- Mechanism involved in the progression of metabolic syndrome and its subsequent transition to CVD and T2DM(diabetes)

- 1. Insulin resistance
- 2. Chronic inflammation
- 3. Neurohormonal activation



ROS-Reactive oxygen species
LOX- lectin-like oxidized low-density lipoprotein receptor-1
RAS- renin-angiotensin system

Increased FFA in muscles

- FFAs affect insulin receptor substrate (IRS-1)-associated PI3K activity, leading to decreased GLUT-4 translocation to the surface and hence reduced glucose uptake.
- Reduction of glycogenesis → hyperglycemia.
- Compensatory hyperinsulinemia causes down regulation of insulin receptor.
- Defects in insulin receptor.

Abdominal obesity

High calorie intake
↓
Adipocyte hypertrophy & hyperplasia
↓
Hypoxia due to reduced blood supply
↓
Necrosis and adipocyte infiltration by overproduction of adipocytokines (FFA, TNF α , IL6, CRP, PAI1)
↓
localized inflammation propagates to systemic inflammation.

Increased FFA in liver & pancreas

- FFAs act on the liver to promote gluconeogenesis and lipogenesis
- The net result is a hyperinsulinemic state to maintain normal glucose levels
- However, the compensation eventually fails, leading to a decrease in insulin levels, which is further exacerbated by the lipotoxic effect of FFAs on beta cells of the pancreas increases.

Insulin resistance

- Insulin is secreted in response to high blood glucose:
 - Inhibiting lipolysis and hepatic gluconeogenesis
 - Increases glucose uptake in liver, muscles, and adipose tissues
- IR in adipose tissue leads to impairment of insulin-mediated inhibition of lipolysis is enhanced in adipose tissue → hydrolysis of stored fats → high plasma FFAs.

Insulin resistance FFA causing atherogenic dyslipidemia

- IR → increased activity of hormone-sensitive lipase → high [FFAs] → increase cholesterol esters and triglyceride (TG) synthesis → increased production of VLDLs
- Cholesterol ester transfer protein (CETP), which promotes the TGs transfer from VLDL to HDL, increasing HDL clearance and decreasing its concentrations
- High VLDL = high LDL

Insulin resistance-hypertension

Hyperglycemia and hyperinsulinemia

↓
Activation of Renin-Angiotensin system (RAS)

↓
Hypertension.

IR and hyperinsulinemia

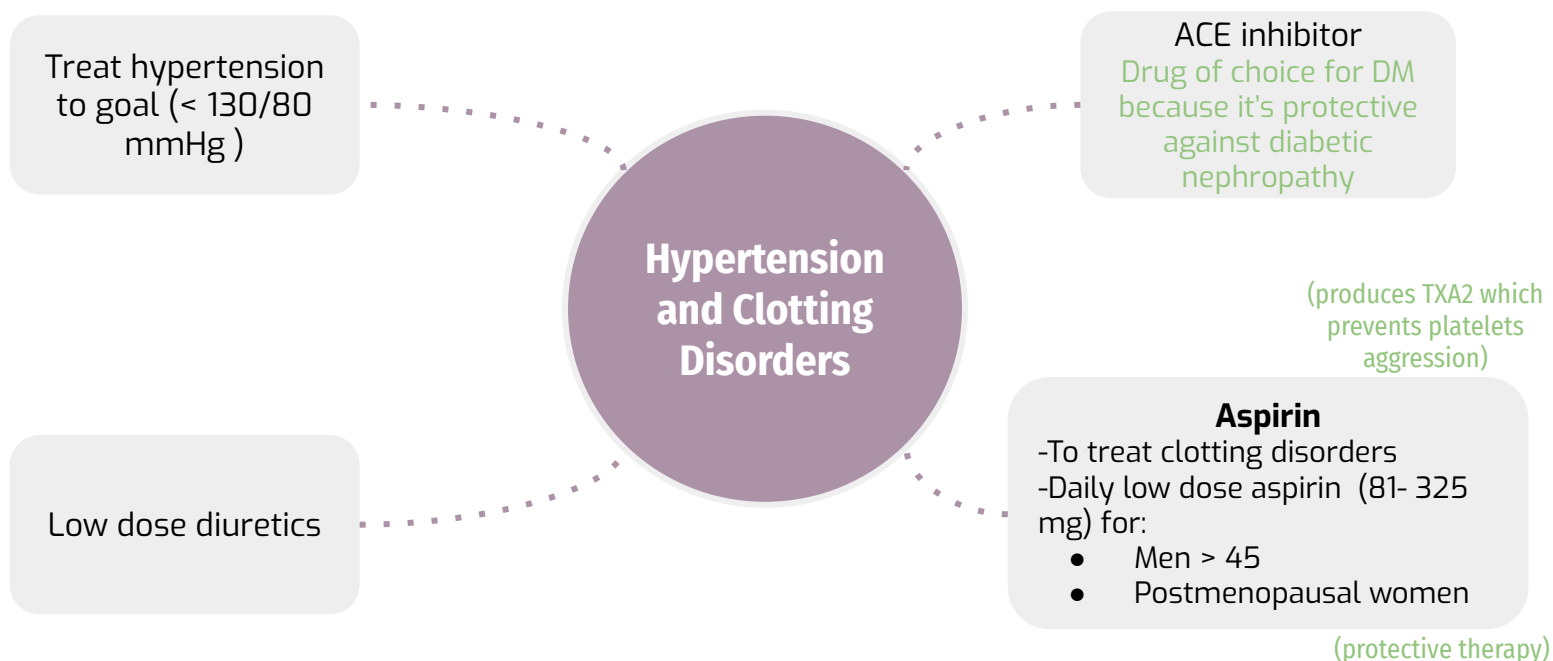
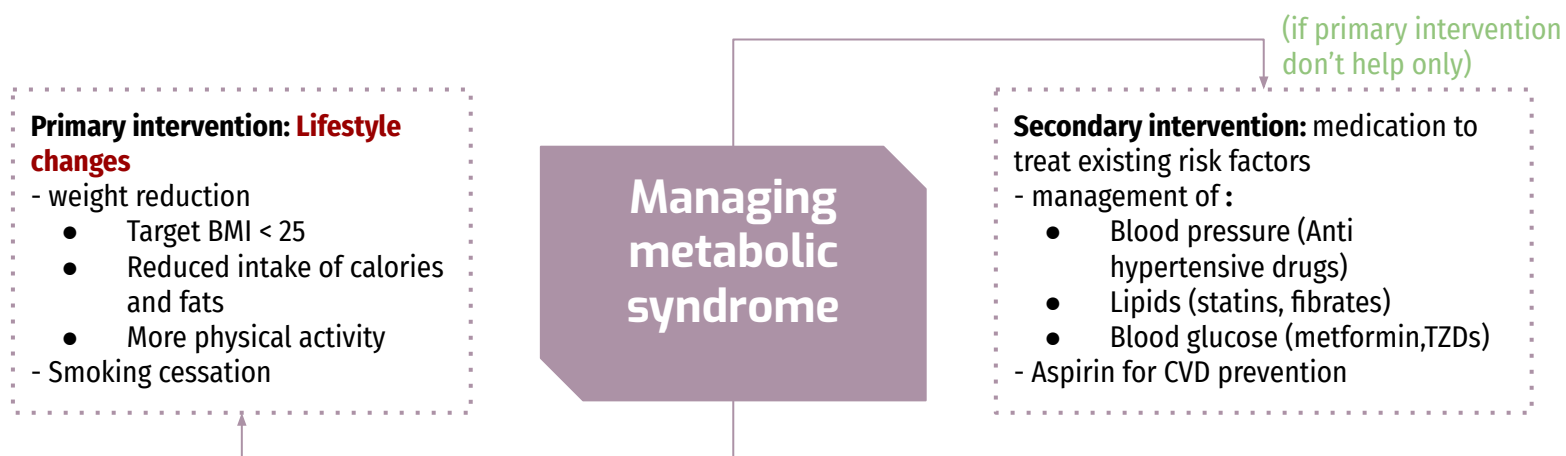
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Stimulation of sympathetic nervous system

↓
Increased renal sodium reabsorption

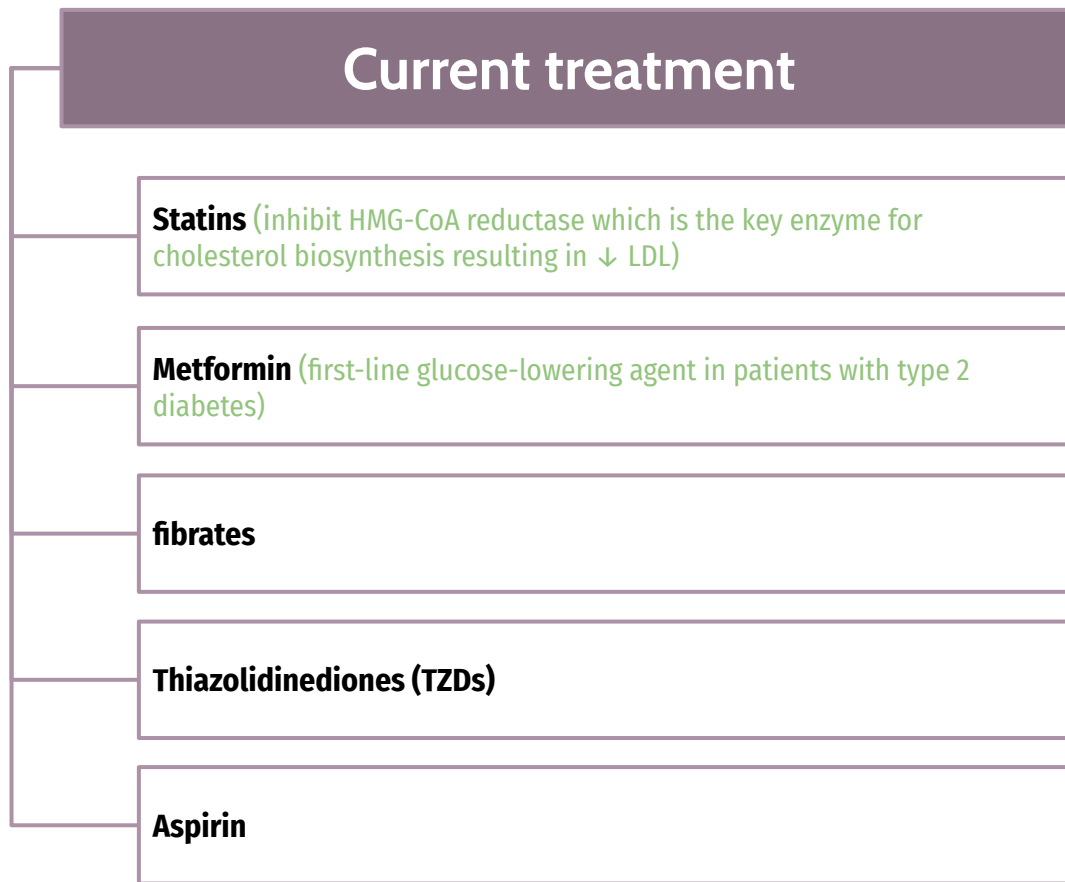
↓
hypertension.

Markers of metabolic syndrome

lipoproteins	adipokines	Inflammatory markers	Hemostatic markers
<ul style="list-style-type: none"> • HDL (low) • LDL (high) 	<ul style="list-style-type: none"> • Leptin (high or normal) • Adiponectin (parallel with HDL levels, so low) 	<ul style="list-style-type: none"> • 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 <p>(All will be high)</p>	<ul style="list-style-type: none"> • Plasminogen activator inhibitor - 1 (PAI 1) <p>Mainly produced by endothelium but also by adipocytes causing fibrinolysis</p> <p>PAI 1 inhibits fibrinolysis. Therefore, in metabolic syndrome people will be more prone to thrombosis</p>

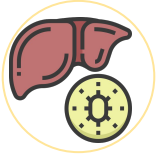


Treatment

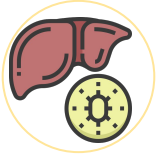


Metformin	Fibrates	Thiazolidinediones (TZDs)
<ul style="list-style-type: none"> • Reduces blood glucose levels inhibiting hepatic gluconeogenesis <ul style="list-style-type: none"> -Hepatic gluconeogenesis is active in patients due to liver's resistance to the effects of insulin • Reduces lipid synthesis in the liver • Helps reducing blood lipids 	<ul style="list-style-type: none"> • Reduce blood lipid levels • Activate transcription factor: <ul style="list-style-type: none"> -Peroxisome proliferator activated receptor-α (PPAR-α) • Activated PPAR-α → transcription of genes of lipid degradation / uptake by the cells: <ul style="list-style-type: none"> -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) 	<ul style="list-style-type: none"> • Used for the treatment of insulin resistance and type-2 diabetes mellitus • TZDs activate PPAR-g (γ) class • of transcription factors expressed primarily in the adipose tissue • Activates the transcription of adiponectin (the good adipokine!) • Adiponectin reduces the fat content of the liver and enhances insulin sensitivity

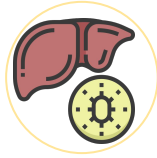
Take home message



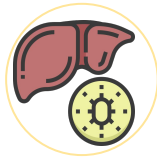
Metabolic syndrome is a combination of metabolic abnormalities that increase the risk of heart disease, diabetes and other diseases



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

Test Yourself!

MCQs

Answers: A-B-C-A

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: 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: List 3 risk factors of metabolic syndrome.

Obesity, smoking, alcoholism.

Q2: List 4 features that comprise the metabolic syndrome?

Obesity, hypertension, insulin resistance, low HDL cholesterol

Q3: Mention 3 abnormalities caused by obesity?

Dyslipidemia, hypertension, insulin intolerance

Meet The Team!

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