Biochemistry Team 435

جامعة الملك سعود
King Saud University 1957

METABOLIC SYNDROME

* Please check out this link to know if there are any changes or additions.

Revised by
هشام الغفيلي & خولة العماري

Color index: Important | Doctors notes | Further explanation.

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.
  - Insulin resistance.
  - Hypertension.

Metabolic Syndrome

❖ A cluster of closely related **medical conditions** which increase the risk of developing **heart disease** and **diabetes**.

Features comprising Metabolic Syndrome:

- **High serum TGs**
- **Hypertension**
- **Obesity** (Specifically **visceral**)
- **Hyperglycemia**
- **Low HDL cholesterol**
- **Hyperinsulinemia** (insulin resistance)

❖ The metabolic abnormalities of obesity reflect molecular signals originating from the **increased mass of adipocytes**.

❖ **The predominant effects of obesity include:**

Next slide

- **Dyslipidemias.**
- **Insulin resistance.**
- **Glucose intolerance**
- **hypertension**

- Cells become **less responsive to insulin** → ***High plasma insulin** "trying to compensate" for years. Eventually, compensation becomes inadequate→ hyperglycemia +:
  - **Hydrolysis** of stored **TGs** or **fats** → High plasma FFA.
  - **Reduction** of glucose uptake or glucose utilization among **muscle cells** + **Reduction** of glycogenesis → **hyperglycemia**.

❖ ***Compensatory hyperinsulinemia** causes **down regulation** of insulin receptors.

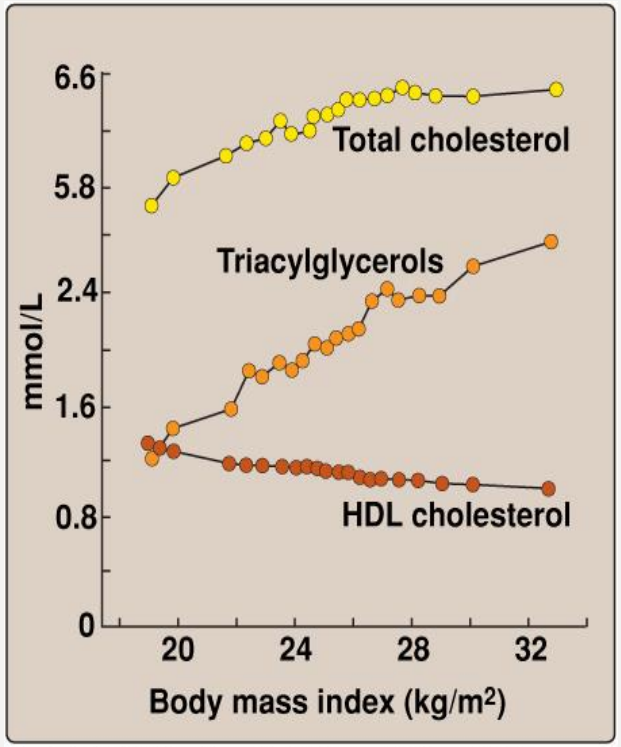
❖ **Defects in insulin receptor.**

Dyslipidemia

Insulin resistance in obese individuals **(adipocytes)** → **Increased** production of insulin in an effort by the body to maintain blood glucose levels → Increased activity of **hormone-sensitive lipase**

Resulting in: **increased** levels of circulating **fatty acids** → fatty acids are carried to the liver and converted to **TGs** and **cholesterol** → **Excess TGs** and cholesterol are released as **VLDL**, resulting in **elevated serum triacylglycerols**.

Concomitantly , HDL levels are decreased.



Increased activity of lipase is because body cannot use glucose as a source of energy, the other source is FFAs which are broken down from triglycerides in adipocytes.

❖ Dyslipidemia and the MetS an inseparable couple?

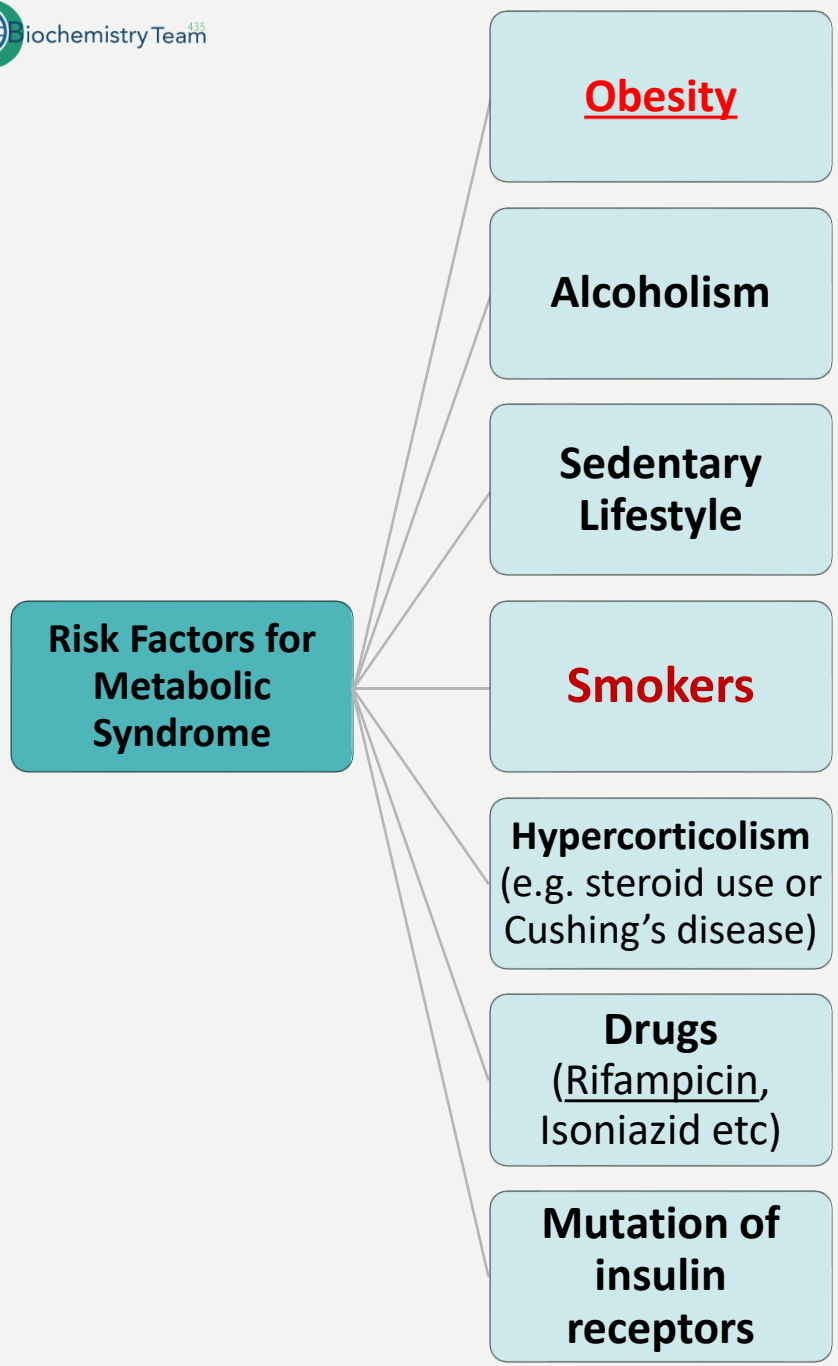
- Dyslipidemia is an **early** indicator and **consistent** component of insulin resistance
- **Liver fat** seems to be the **unifying factor** between **dyslipidemia** and **insulin resistance**

If a patient has dyslipidemia, he has insulin resistance for sure!

Biochemistry Team

Metabolic Syndrome is Linked to:

- **Heart disease** → 1 .5 - 3 fold increase for **atherosclerotic CVD**
- **Type 2 Diabetes Mellitus** → 5 fold increase ← it starts as an insulin resistance then develop into DM over time.
- **Kidney disease**
- **Reproductive abnormalities in women** → **PCOS**, **difficulty** with ovulation and fertility, **irregular periods** ← One of the causes of infertility in women is insulin resistance. PCOS: polycystic ovarian syndrome
- **Nonalcoholic steatohepatitis (fatty liver)** → Related to **distorted lipid metabolism**
- **Cancer** → **Obesity** is major risk factor for cancer of the esophagus; colon and rectum; liver; gall bladder etc → Being overweight and obese accounts for **14%** of all cancer deaths in men and 20% of those in **women**



Markers of Metabolic Syndrome

Lipoproteins	LDL	high
	HDL	low
	TGs	High
Adipokines	Leptin	increased or no change
	Adiponectin	decreased
Inflammatory markers	CRP	High
	TNF-a	
	IL-6	
	IL-8	
Hemostatic marker	Plasminogen Activator inhibitor-1	Present (it's high → increases the chance of atherosclerosis)

note: obese people are always in state of invisible inflammation due to the release of inflammatory markers

DIAGNOSIS:

WHO criteria (1999)		NCEP* ATP** III Guideline (2002)	
One of: Impaired glucose tolerance - DM - insulin resistance along with at least **two** of the below mentioned components يكون عندهم وحدة من ال٣ اشياء اللي فوق بالإضافة الى خاصيتين من:		**≥ 3** of these risk factors are present يكون عندهم ٣ أو أكثر من الرسك فاكتورز:	
Component	Criterion	**Waist circumference:**	• Men>102 cm (>40 in) • Women>88 cm (>35 in
Hypertension	BP >140/90 mmHg	**Triglycerides:**	>150 mg/dL
Dyslipidemia	High plasma TGs (>1.7mmol/L) Low HDL cholesterol (men <0.9, women <1.0 mmol/L)	**HDL cholesterol:**	• Men<40 mg/dL • Women<50 mg/dL
Central or Genenral obesity	Waist to hip ratio >0.9 in men, >0.85 in women And/or BMI >30	**Blood pressure**	130/ 85 mm Hg
Micro-albuminuria	Urinary albumin excretion rate ≥ 20ug/min or albumin:creatinine ratio ≥ 30mg/g	**Fasting glucose**	>100 mg/dL

Dr. Sumbul: you don't have to memorize the numbers! Ranges will be given in the exam!

They can ask us: which one of the following is a component of WHO criteria?

*National Cholesterol Education Programme
** Adult Treatment Panel

Management of metabolic syndrome:

Primary intervention:(Lifestyle changes)

- **Smoking cessation**
- **Weight reduction**

(strive for BMI less than 25)

- **Reduced** caloric intake and dietary fat.
- **Increased** physical activity
- Set realistic goals: 5-10% weight loss from baseline

Secondary intervention: Pharmacotherapy

1-Hypertension and clotting disorders

- **Anti-hypertensives**
- **Aspirin for CVD prevention**

3- Dyslipidemia

- statins
- **fibrates**

2-Hyperglycemia

- **metformin**
- **TZDs**

secondary intervention is used when metabolic syndrome cannot be controlled primarily, so we control the symptoms.

Biochemistry Team

LOWERING BLOOD PRESSURE

Modification	Recommendation	Average drop on SBP
Weight Loss	Maintain normal **body weight**	5-10 for every 22lbs loss
Healthy eating plan	**Meal plan** rich in **fruits**, **vegetables**, **low fat dairy** and **low** in **saturated fat** and **cholesterol**	8-14 نلاحظ ان الشخص لو حافظ على غذاء صحي بينزل السستولك برشر ٨-١٤ وتأثيره اعلى من الباقيين
Sodium Restriction	Less than 2400 mg/day (only sodium, not the salt. Because salt is composed of Cl & Na)	2-8
Regular physical activity	30 min most days of the week	4-9

1-HYPERTENSION AND CLOTTING DISORDERS

Hypertension:	Clotting disorders:
Treat hypertension to goal (<130/80 mmHg)	➢ **Aspirin-** to treat clotting disorders ✓ Daily **low dose aspirin** (81-325mg) for men over age 45 and postmenopausal women.
Low dose diuretic.	
ACE inhibitor (if also have **DM**).	

*No particular agent is preferred for **metabolic syndrome**.

نوع المانجمنت هنا سكندري ولا برايمري؟ سكندري..
ليش؟ لأننا قاعدين نستخدم الأدوية علشان نتحكم بالرسك فاكتورز "ارجعوا للمايند الماب اللي بالسلايده السابقة"

2-HYPERGLYCEMIA

	Metformins	Thiazolidinediones (TZDs)
Uses :	In patients with type 2 diabetes who are obese (first line therapy).	Used for the treatment of **insulin resistance** and **type 2 diabetes mellitus** e.g. pioglitazone
MOA :	➢ **Reduces lipid synthesis** in the liver which aids in modulating blood lipid levels in these patients. من الايجابيات بهالدواء ان له تأثير على اللبدز فممكن انه يضبط الدسلبديميا	• TZDs activate **PPAR-γ** class of transcription factors expressed primarily in the adipose tissue. • Activates the transcription of **adiponectin** • The increase in **adiponectin reduces** the fat content of the liver and **enhances insulin sensitivity**.
	➢ **Reduces blood glucose levels** by inhibiting hepatic gluconeogenesis Hepatic gluconeogenesis is active in patients due to liver's resistance to the effects of insulin. الكبد ماراح تستجيب للانسولين بسبب الرزستنتس فالجلوكونيوجنسس ماعندها مين يردعها ويقولها "لا" فبتكون اكتف وبتزداد نسبة الجلوكوز بالدم.. الميتافورمن بيجي وبتثبط هالجلوكونيوجنسز "بيردعها وبيوقفها عند حدها!" فبالتالي بيحد من الهايبرجلايسيما!	

3-DYSLIPIDEMIA

❖ Fibrates

Used to:	**Reduce the lipid levels.**
Mechanism:	➢ Target for fibrates is **a transcription factor-** peroxisome proliferator activated receptor-**α** "الفا موب قاما!!" ➢ **PPAR- α** when activated, leads to the transcription of genes involved in **lipid degradation**, or **uptake by the cells**. E.g. • **Carnitine:** palmitoyl transferase I- enhances the uptake of FA into the mitochondria. • **Lipoprotein Lipase** • Stimulates **apoAI** and **apoAII** protein synthesis (major proteins in **HDL**)

- End of endocrine biochemistry! ✨-

Check your understanding!

Q1: which one is not a risk factor of metabolic syndrome ?

A. Alcoholism
B. .hypertension
C. Atherosclerosis
D. Obesity

Q2: which one of the following in not an abnormality caused by obesity ?

A. Dyslipidemia
B. .high HDL
C. Hypertension
D. DM

Q3:which one of the following criteria fits to diagnose with metabolic syndrome depending on who?

A. DM + hypertension only
B. .DM + HTN + high HDL
C. DM + HTN + low TGs
D. DM + HTN + Microalbuminemia

Q4: What is the mechanism of action of TZDs ?

A. Activates PPAR-alpha
B. .activates PPAR-gamma
C. In hepatocytes to increase excretion
D. In duodenum to decrease the absorption

Q5: which one of the following is an inflammatory marker of metabolic syndrome ?

A. interleukin-2
B. .interleukin-4
C. interleukin-6
D. interleukin-1

Q6: Which one of the following is true about dyslipidemia ?

A. High HDL
B. .High VLDL
C. A+B
D. LOW VLDL

1.C 2.B 3.D 4.B 5.C 6.B

Check your understanding!

Q7: Which one of the following drug inhibit gluconeogenesis ?

A. Metformin
B. Fibrates
C. Aspirin
D. Statin

Q8: which one of the following may occur in a female patient with metabolic syndrome ?

A. Malnutrition
B. Anemia
C. POS
D. Addison's disease

Q9: In metabolic syndrome, What is the main organ that plays a major role in causing dyslipidemia?

A. liver
B. .kidney
C. Waist adipocyte
D. Brest adipocyte

Q10: AS a pathophysiology of dyslipidemia, excessive amount of triglycerides\cholesterol is released from the liver in the blood in from of ?

A. HDL
B. .VLDL
C. Chylomicron
D. Bilirobin

Q11: Which one is hemostatic marker for metabolic syndrome ?

A. leptin
B. .CRP
C. PAI-1
D. TNF-a

Q12: which one of the following consider primary intervention in management ?

A. anti-hypertnesive
B. Statins
C. Smoking cessation
D. aspirin

7.A 8.C 9.A 10.B 11.C 12.C

Done by:

–شهد العنزي.

– عبدالله الغزي.

– ابراهيم الشايع.

– لينا الشهري.

– نوف الرشيد.

Revised by:

–منيرة العمري.

Resources:

- 435's slides & notes.

@435biochemteam

435biochemistryteam@gmail.com

@biochemteam435