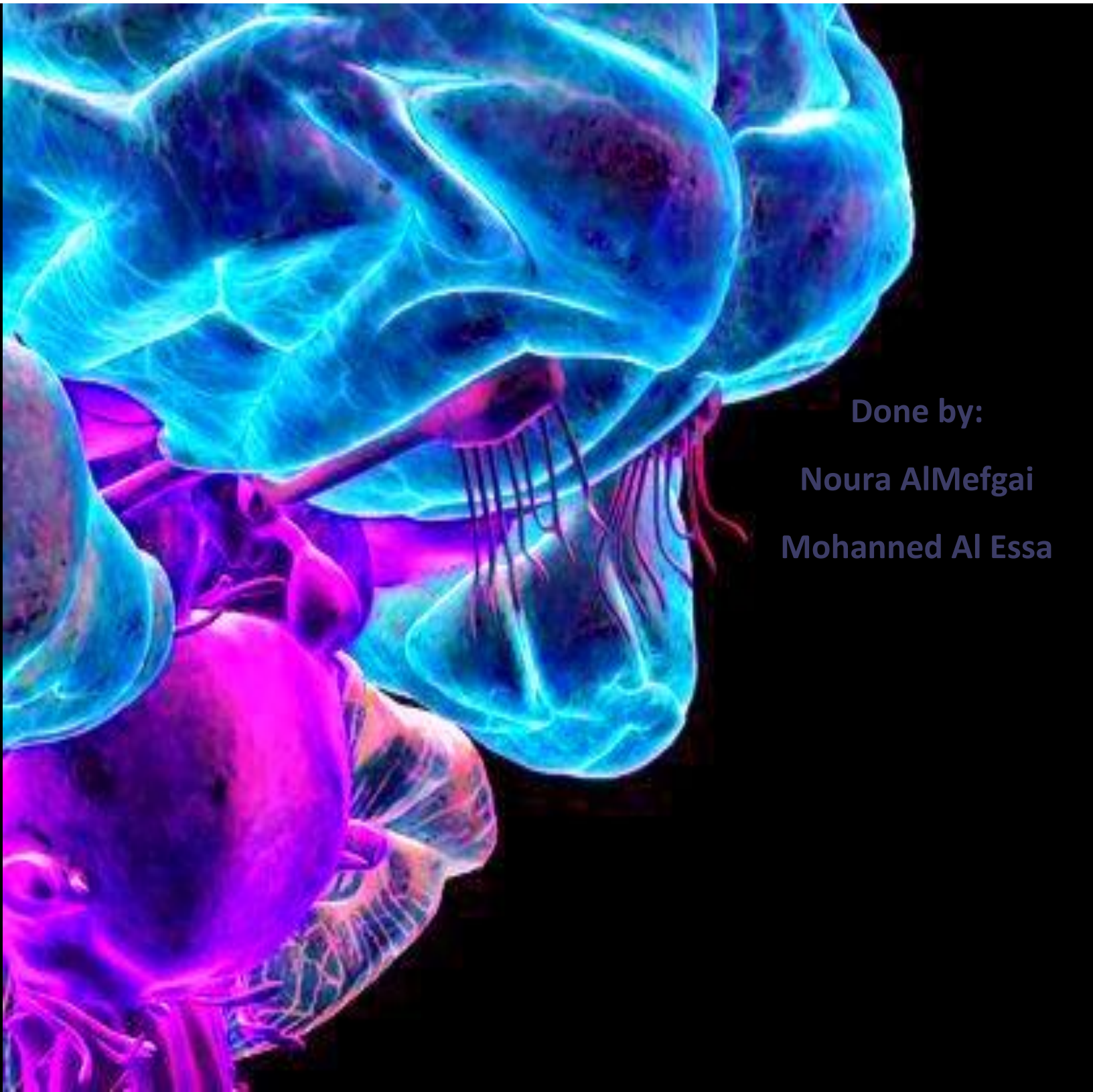


Metabolic Syndrome



Done by:

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- A combination of metabolic abnormalities which increase the risk of heart disease, diabetes and other diseases
- Obesity is a component of metabolic syndrome
- Signals from adipocytes in obesity cause metabolic abnormalities such as:
 - Dyslipidemia
 - Glucose intolerance
 - Insulin resistance
 - Hypertension

Features of metabolic syndrome

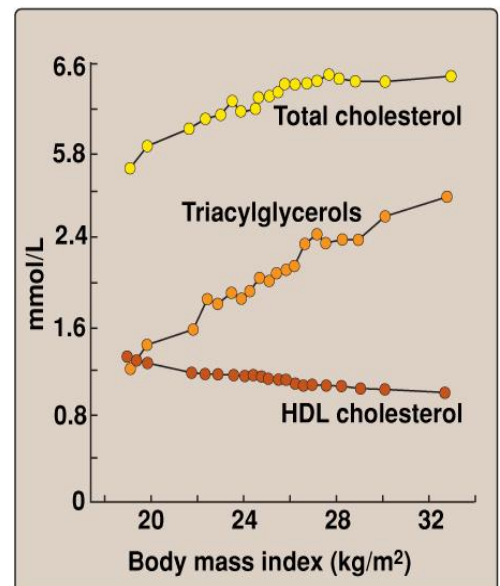
- Obesity
- High serum triglycerides (TGs)
- Low HDL cholesterol
- Hypertension
- Hyperglycemia
- Insulin resistance (hyperinsulinemia)

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

Dyslipidemia

- Insulin resistance 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
- **insulin has an antiglycolytic activity, it decrease the carbon sensitive lipase enzyme in the adipocyte so it stops the breakdown of TG in the adipose tissue, when there is insulin resistance there is an increase in the activity of the hormone sensitive lipase in the adipocytes which will lead to the breakdown of TG to FFAs that will go to the circulation then to the liver where they will be converted to TG and cholesterol then they'll get released as VLDL.**



Dyslipidemia and met. Synd. 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 for Metabolic Syndrome:

- Obesity
- Alcoholism
- Sedentary Lifestyle
- Smoking
- Hypercortisolism (Steroid use/Cushing's disease)
- Drugs (Rifampicin, isoniazid, etc.) they increase the body weight.
- Mutations in insulin receptor

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, gall bladder
 - 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

PLUS any of these two:

The first three should be present in the diagnosis

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

NCEP ATP III Guideline (2002)

The more accurate one.

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 know the numbers but you don't need to memorize them because they will be given

Markers of metabolic syndrome:

- Lipoproteins (LDL, HDL)
- Adipokines (Leptin, adiponectin)
- Inflammatory markers. Obesity is a chronic low grade inflammation.
 - c-reactive protein, TNF-α, IL-6, IL-8
- Hemostatic marker
 - Plasminogen activator inhibitor-1. inhibits the fibrinolysis (normal degradation of the clots)

Managing Metabolic Syndrome

- Primary intervention: Lifestyle changes
 - Weight reduction
- Target BMI < 25
- Reduced intake of calories and fats

- More physical activity
 - Smoking cessation
- 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 loss
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
- Aspirin:
 - To treat clotting disorders
 - Daily low dose aspirin (81-325mg) for:
- Men > 45
- Postmenopausal women

Current Treatment

- Statins
- Metformin
- Fibrates
- Thiazolidinediones (TZDs)
- Aspirin

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:
 - Peroxisome proliferator activated receptor- α (PPAR- α)
- Activated PPAR- α \rightarrow transcription of genes of lipid degradation / uptake by the cells:
 - Carnitine: palmitoyl transferase I (enhances FA uptake into mitochondria)
 - Lipoprotein Lipase
 - Stimulates apoAI and apoAII protein synthesis (major proteins in HDL)

Thiazolidinediones (TZDs)

- Used for the treatment of insulin resistance and type-2 diabetes mellitus
- TZDs activate PPAR- γ 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

Summary

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Current Treatment Statins, Metformin, Fibrates, Thiazolidinediones (TZDs), Aspirin