Metabolic Syndrome

DOPE'amines
COGS 163

Overview

- Metabolic Syndrome
  - General definition and criteria
  - Importance of diagnosis
- Glucose Homeostasis
- Type 2 Diabetes Mellitus
- Insulin Resistance
  - Testing for Insulin Sensitivity
  - Free Fatty Acids (FFA)
  - Causes & Pathways
- Lifestyle Choices and Treatment

Metabolic Syndrome

Definition*:

A set of associated symptoms characterized by “physiological, biochemical, clinical, and metabolic factors that directly increases the risk of cardiovascular disease, type 2 diabetes mellitus”

*It is important to note that the definition of MetS is still being constructed as there is not a singular definition for it due to *slight* differences in criteria.

From Review of Metabolic Syndrome_Kaur

Metabolic Syndrome Diagnosis Criteria

1. Abdominal obesity
2. Dyslipidemia
    a. Abnormally elevated cholesterol or fats (lipids) in the blood
3. Hypertension
    a. Abnormally high blood pressure
4. Impaired Glucose Homeostasis

- Not all symptoms are required for diagnosis*
- Symptoms can arise in any chronological order
- *Different definitions (next slide)

Table 15.3 Summary of the criteria for the metabolic syndrome.

Risk factor		Categorical cutpoints
Waist circumference		
	Men:	≥40 in., ≥102 cm
	Women:	≥35 in., ≥88 cm
TGs		≥150 mg/dL (1.7 mmol/L), or drug therapy for elevated TGs
HDL		
	Men:	<40 mg/dL (0.9 mmol/L)
	Women:	<50 mg/dL (1.1 mmol/L), or drug therapy for low HDL
BP		Systolic BP ≥130 mmHg, or diastolic BP ≥85 mmHg, or current antihypertensive therapy
Fasting glucose		≥100 mg/dL, or drug therapy for elevated glucose [11]

From “Insulin Resistance, Metabolic Syndrome, and Therapy”

*Different Criteria for Metabolic Syndrome

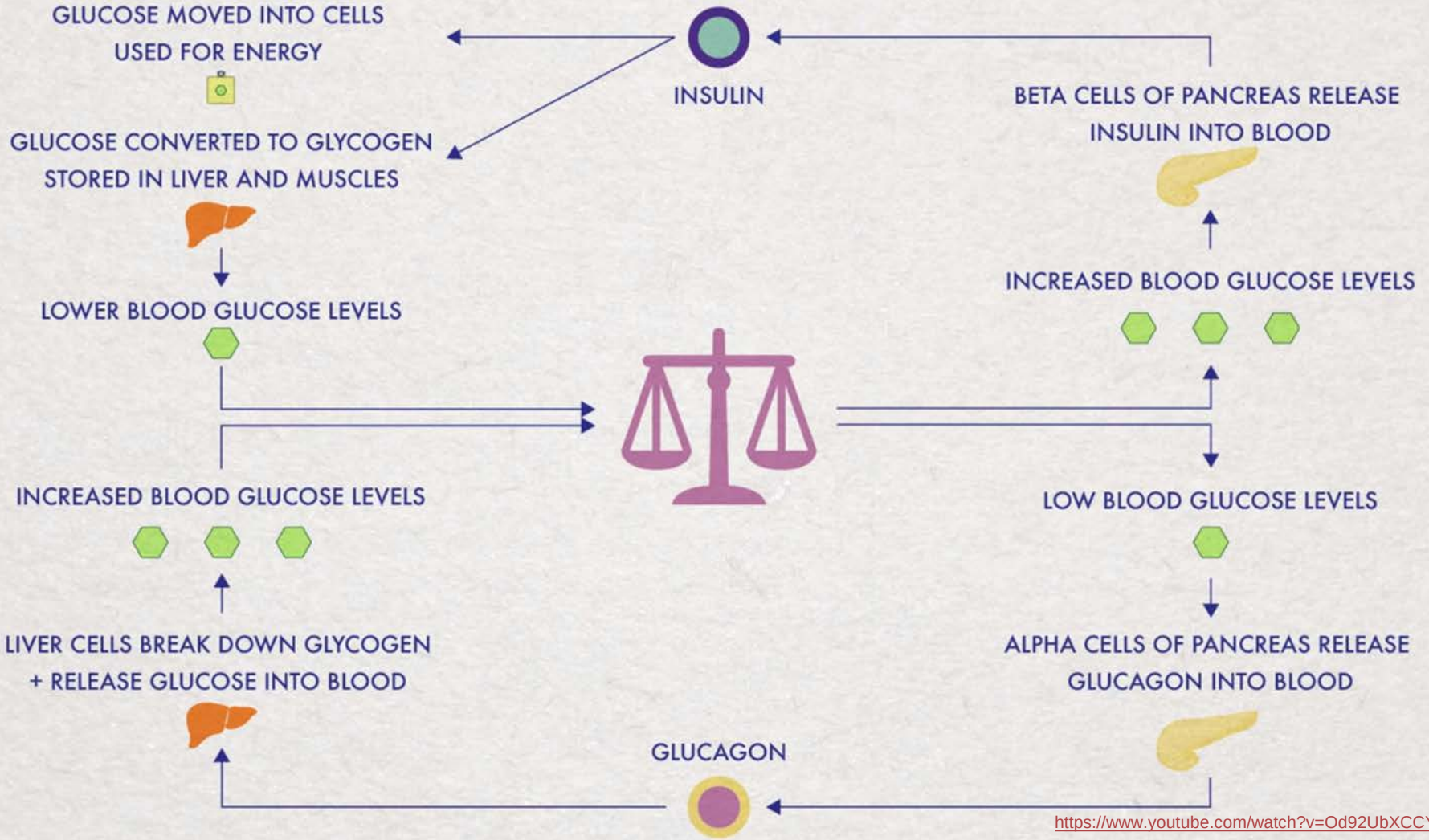
Table 1: Diagnostic criteria proposed for the clinical diagnosis of the MetS.

Clinical measures	WHO (1998) [5]	EGIR (1999) [6]	ATPIII (2001) [7]	AACE (2003) [8]	IDF (2005) [9]
Insulin resistance	IGT, IFG, T2DM, or lowered insulin Sensitivity[a] **plus any 2 of the following**	Plasma insulin >75th percentile **plus any 2 of the following**	**None, but any 3 of the following 5 features**	IGT or IFG **plus any of thefollowing based on the clinical judgment**	None
Body weight	Men: waist-to-hip ratio >0.90; women: waist-to-hip ratio >0.85 and/or BMI > 30 kg/m^2	WC ≥94 cm in men or ≥80 cm in women	WC ≥102 cm in men or ≥88 cm in women	BMI ≥ 25 kg/m^2	Increased WC (population specific) **plus any 2 of the following**
Lipids	TGs ≥150 mg/dL and/or HDL-C <35 mg/dL in men or <39 mg/dL in women	TGs ≥150 mg/dL and/or HDL-C <39 mg/dL in men or women	TGs ≥150 mg/dL HDL-C <40 mg/dL in men or <50 mg/dL in women	TGs ≥150 mg/dL and HDL-C <40 mg/dL in men or <50 mg/dL in women	TGs ≥150 mg/dL or on TGs Rx. HDL-C <40 mg/dL in men or <50 mg/dL in women or on HDL-C Rx
Blood pressure	≥140/90 mm Hg	≥140/90 mm Hg or on hypertension Rx	≥130/85 mm Hg	≥130/85 mm Hg	≥130 mm Hg systolic or ≥85 mm Hg diastolic or on hypertension Rx
Glucose	IGT, IFG, or T2DM	IGT or IFG (but not diabetes)	>110 mg/dL (includes diabetes)	IGT or IFG (but not diabetes)	≥100 mg/dL (includes diabetes)[b]
Other	Microalbuminuria: Urinary excretion rate of >20 mg/min or albumin: creatinine ratio of >30 mg/g.			Other features of insulin resistance[c]	

From Review of Metabolic Syndrome_Kaur

Importance of Diagnosis

- The diagnosis of Metabolic Syndrome may:
  - Indicate a predisposition to greater risk for developing Type 2 Diabetes
  - Identify individuals that are at higher risk for Cardiovascular Disease (CVD)
- Diagnosing MetS may help with earlier detection and earlier intervention to potentially improve prognosis
  - Goal: minimize risk factors leading to Type 2 Diabetes and Cardiovascular Disease



https://www.youtube.com/watch?v=Od92UbXCCYI

Glucose Homeostasis

1) Insulin secretion by pancreatic beta cells
- eating → insulin etc. (cephalic phase)

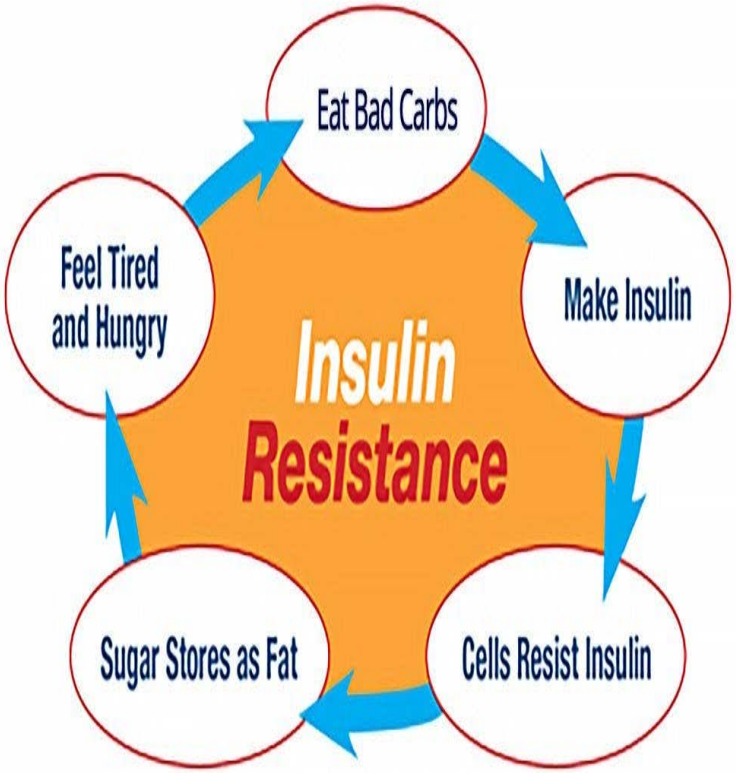
2) Suppression of liver glucose production by by blocking glycogenolysis and gluconeogenesis

3) Stimulation of glucose uptake by liver, skeletal muscle, and adipose tissues

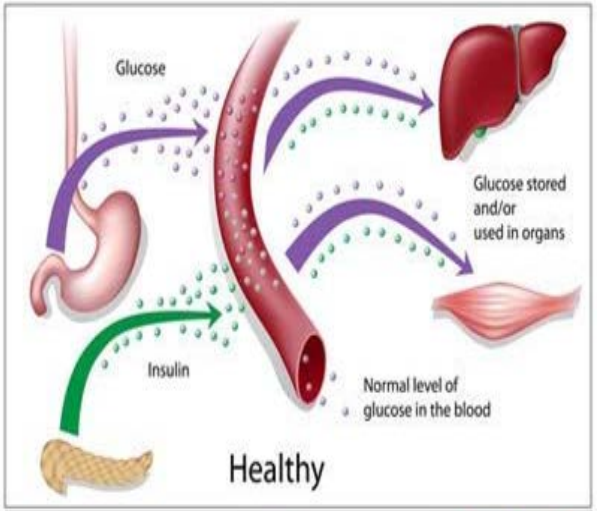
Type 2 Diabetes Mellitus

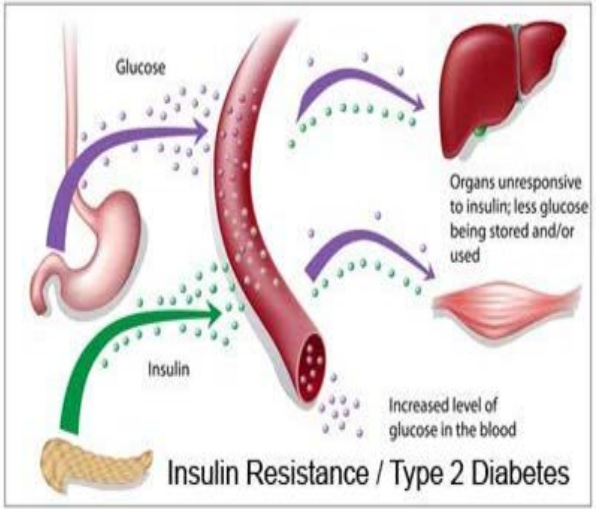
- High glucose blood levels due to deficiency in production or function of insulin
- Amount of people with T2D tripled over past 30 years
- High prevalence of Metabolic Syndrome before T2D
  - Risk 5x greater
- Glucose Criteria:
  - Fasting plasma glucose (WHO) $\geq$ 126 mg/dL
  - Non-fasting plasma glucose or symptoms of hyperglycemia $\geq$ 200 mg/dL
  - 2-hour plasma glucose during an oral GTT $\geq$ 200 mg/dL
  - Hemoglobin A1C $\geq$ 6.5%

Insulin Resistance



https://www.dietdoctor.com/why-insulin-resistance-is-good





http://goodfoodeating.com/4321/what-is-insulin-resistance/

Testing for Insulin Resistance

- Hyperinsulinemic - euglycemic Clamp
  - Prolonged insulin infusion to keep insulin levels constant
  - Repeated blood sampling
  - Glucose added to counter effects of insulin and to keep insulin constant
  - Amount of glucose added → insulin resistance measure
- Oral Glucose Tolerance Test (2 hour post-glucose challenge)
  - Repeated blood sampling
  - Glucose levels tested just before and then 2 hours after
- Fasting insulin level measures:
  - HOMA - Homeostasis Model Assessment
  - QUICKI - Quantitative insulin sensitivity index
  - FGIR - Fasting glucose to insulin ratio
  - FIGP - Fasting insulin glucose product

Insulin Resistance and FFAs

- Adipose Tissue
  - More adipose tissue mass increases the turnover of Free Fatty Acids (FFA) through lipolysis
  - Insulin inhibition of adipose tissue lipolysis
    - Under insulin resistance: unable to regulate lipolysis
    - High FFA levels reinforces insulin resistance
  - Adipose tissue also excessively releases proinflammatory cytokines
  - Decrease in adiponectin/ adipogenesis
- Skeletal Muscle
  - Reduction in insulin sensitivity by inhibiting insulin-mediated glucose uptake
  - Impaired mitochondrial oxidative capacity and biogenesis

Insulin Resistance and FFAs (continued)

- Liver
  - Numerous models have shown increases in FFA impair hepatic insulin action
  - High FFAs enhances very low density lipoprotein (VLDL) synthesis and secretion
    - Increases triglyceride synthesis and storage
    - Associated with dyslipidemia (MetS)
- Cardiovascular
  - Atherosclerosis: build up of plaque in arteries
  - Increased vascular inflammation

Causes of insulin resistance

- Low birth weight due to prenatal stress and increased HPA axis activity leading to insulin resistance and MetS
- Medications (antidepressants, antipsychotics) related to gain of adipose tissue
  - HIV drug therapy functions through adipose inflammation, severe mitochondrial dysfunction, and increased oxidative stress all implicated in insulin resistance
- Stress increases hypothalamic arousal:
  - Cortisol release → inflammation → insulin resistance → MetS
  - Activation of sympathetic nervous system → oxidative stress, inflammation → insulin resistance → MetS
- Overweight → physical inactivity and prevalence

Causes of insulin resistance (cont.)

- Genetics
  - Implication of hunter-gatherers and periods of food scarcity allows for conservation of energy
  - BUT: now excess in diets + physical inactivity → MetS
  - Environmental factors to play a role
- Aging
  - Chronological aging → loss of lean body mass replaced with adipose tissue; less muscle decreases amount for glucose disposal; physical inactivity and/or sedentary lifestyle is a cause for acceleration
  - Physiological aging
    - Cells look old;
  - Telomere reduction - accelerates if you have poor health
    - Cells are getting older
- Physical inactivity
  - Reduced fatty acid oxidative capacity, reduced skeletal muscle blood flow
  - Insulin sensitivity correlates with cardiovascular fitness

Biological Mechanisms of Insulin Resistance

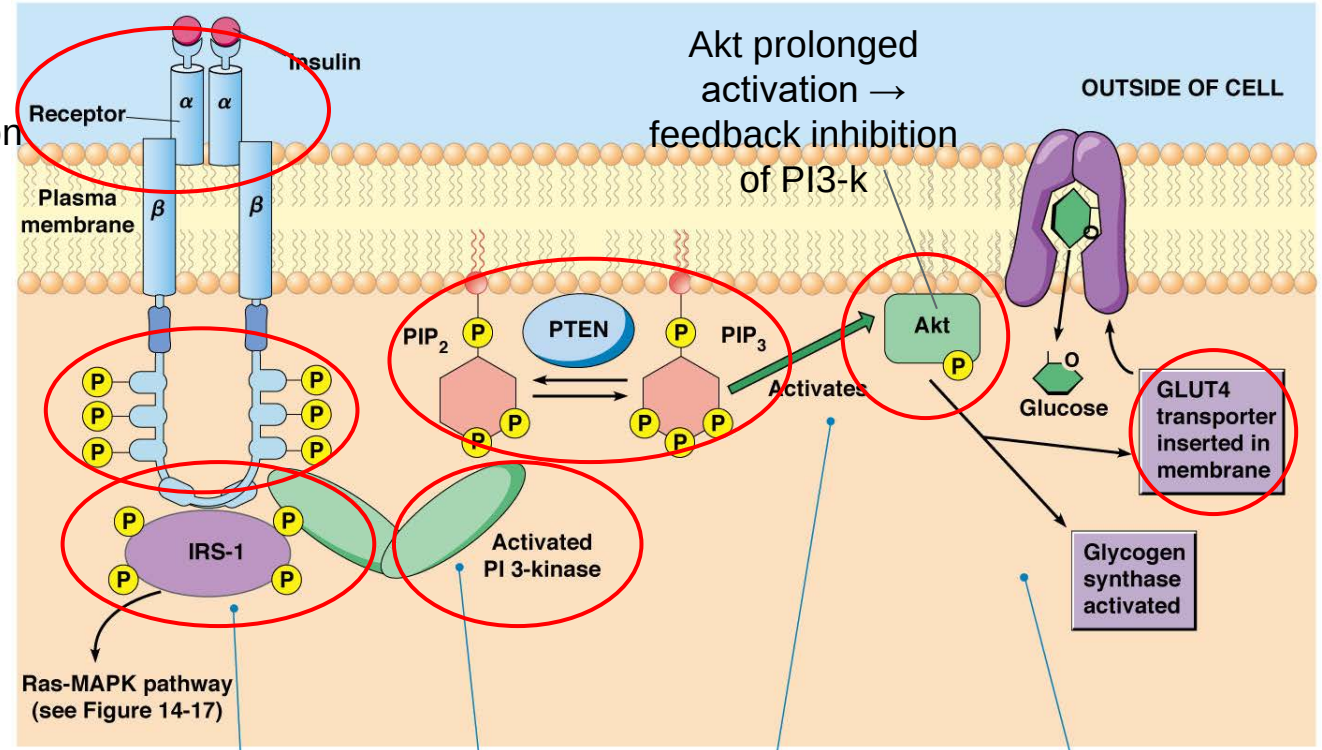
- No single cause of insulin resistance
- Two general ideas:
  - Insulin receptor becomes abnormal
  - Insulin signaling becomes dysfunctional
    - Dephosphorylation of normally phosphorylated compounds
      - Adding phosphate→ activation
      - Deactivation → block action→ terminate signal
    - Feedback inhibition
    - Impaired glucose transport responses

Receptor phosphorylation capacity diminished

Tyrosine-P of IRS prevented by serine-P, which impairs IRS signaling

Tyrosine phosphatases dephosphorylate insulin receptor, terminate signal

- Obesity



IRS expression reduced

- Obesity

Impaired activity

Impaired insulin-stimulated activation of Akt and atypical PKC

- Glucose transporter
- PKC deficient in muscle; in liver, increases lipid synthesis

In liver, TRB3, a protein normally inhibited in presence of glucose, is active and inhibits and blocks Akt

Biological Pathways to Insulin Resistance

- Most lead positive feedback loops that deepen insulin resistance

1) Cell Senescence
2) Mitochondrial dysfunction
3) Telomere attrition
4) Oxidative Stress
5) Inflammation
6) Fox proteins and Sirtuins
7) Free Fatty Acid (FFA) Flux
8) Ectopic Fat
9) Endothelial dysfunction
10) Hepatic Dysfunction
11) Hyperglycemia

Cell Senescence

- Cells stop dividing
- Caused by dysfunctional cellular infrastructure
  - Mitochondrial dysfunction, telomere attrition, ER stress
- Impairs normal functioning, antioxidant defenses, DNA repair systems
- *Proinflammatory phenotype favoring insulin resistance
  - Further mitochondrial and telomeric impairment

Inflammation*

1) Stimulates stress pathways
2) Impairs mitochondrial functions
3) Suppresses adiponectin (regulates blood glucose levels in adipose tissue)
4) Increases cortisol release

- Also cyclic
- Inhibiting IRS-1 activation
- Decreased PI3-Kinase activation
- Decreased GLUT 4 translocation

Mitochondrial dysfunction

- High fitness
- Decline in density and function
- Increased by stress, aberrant insulin signaling, abnormal glucose use, Type 2 DM
- Fewer and smaller sized mitochondria in skeletal muscle of insulin-resistant, obese, or Type 2 DM patients
- Affected by: aging, overnutrition, obesity (decreases mitochondrial expression, function, and biogenesis)
- Decreased energy production from oxidative phosphorylation
- Vicious cycle

FFA

- Link between nutrient excess, dysfunctional obesity, and systemic insulin resistance
- Affect glucose production in many different ways
  - Hepatic, vascular, immune, etc.
- High plasma FFAs → FFA uptake by Beta cells → lipotoxicity→ loss of Beta cell function→ insulin impairment→ apoptosis (cell death)

Interconnected

Box 15.7 Pathways leading from predisposing factors to cardiometabolic and related disease

				Mitochondrial dysfunction		NAFLD
Genetics				Telomere attrition		Dyslipidemia
Physical inactivity				Oxidative stress		Type 2 DM
Physiologic aging				Inflammation		Hypertension
Dysfunctional obesity	→	Insulin	→	Fox dysregulation	→	CHD
Stressors		resistance	←	FFA flux	←	Other vascular disease
Low birth weight				Ectopic fat		Cardiomyopathy
Medications				Endothelial dysfunction		PCOS
				Hepatic dysfunction		Malignancies

From “Insulin Resistance, Metabolic Syndrome, and Therapy”

Treatment: Therapeutic Lifestyle Changes (TLCs)

1) Weight Control
    a) Even small weight loss can significantly reduce triglycerides & BP
2) Healthy Diet
    a) "Mediterranean" and "DASH" diet
    b) Reduce intake of simple sugars but complex sugars good
    c) Calorie restriction can restore mitochondrial function
3) Physical Activity
    a) Reduces insulin resistance and skeletal muscle lipid levels
    b) impact on insulin sensitivity evident for 24 to 48 hrs, disappears in 3-5 day → recommended at least 30 min/day most days of week

Treatment: Therapeutic Lifestyle Changes (TLCs) (cont.)

- "TLCs are more effective than drug therapy in improving insulin sensitivity" (Insulin Resistance, Metabolic Syndrome, and Therapy)
  - DPP trial results
- However, these lifestyle changes can be complemented by pharmaceutical medications that are insulin sensitizing
  - Comorbidities: hypertension, vascular disease, cardiomyopathy

Treatment: Medication

- Lifestyle changes are very difficult to make
- Drugs used as a more reliable, easier method to help, aided by lifestyle changes
- Common Medications:
  - Metformin → "preferred first line therapy" for patients with type 2 DM
    - Decreases cardiovascular risk & delay onset
    - Helps to control amount of glucose in your blood
    - Helps increase body's response to insulin
      - Activates AMPK → enzyme that improves insulin sensitivity, glucose uptake, lipid profile
  - TZDs → synthetic ligands that activate PPAR-gamma, which regulates expression of specific genes in fat cells & mostly found in adipose tissue
    - Reduces insulin resistance
    - Can also increase production of adiponectin
  - Statins → most effective for reducing low density lipoprotein cholesterol (LDL-C)
    - Shown to reduce incidence of heart attacks by more than 33% in patients with coronary artery disease
- **Medication effects can be increased with lifestyle changes

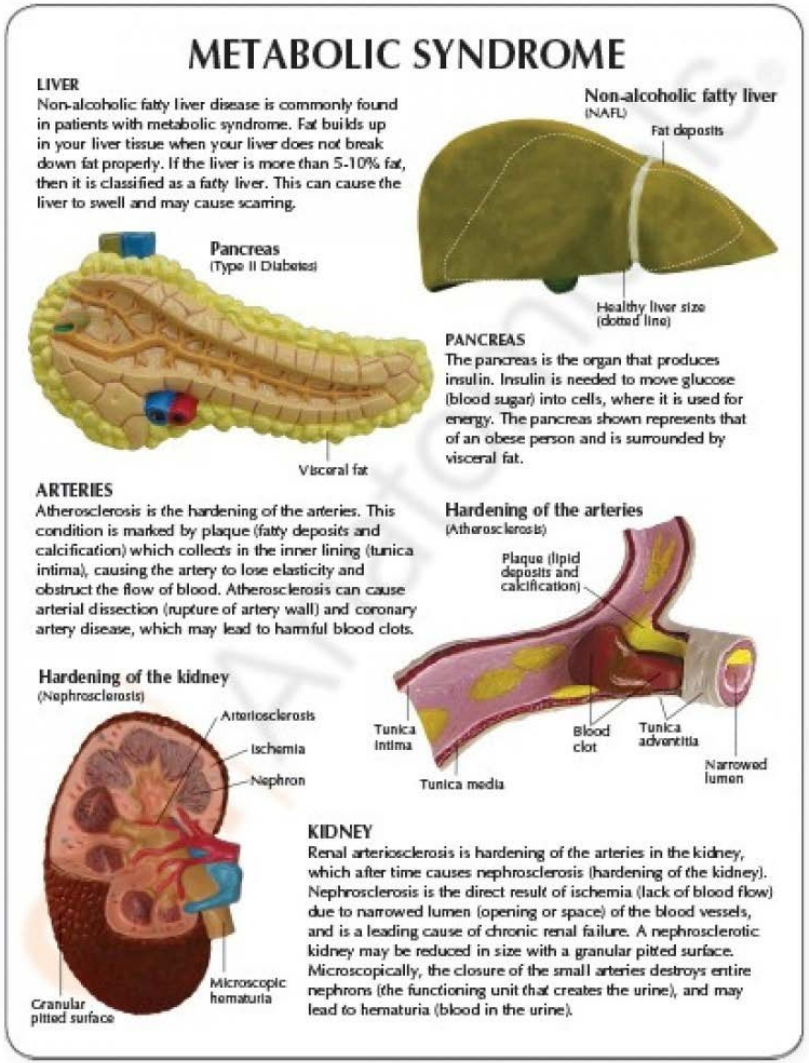
Summary

Metabolic syndrome is a set of symptoms that co-occur and increase the risk of CVD and T2DM

Insulin resistance is a primary pathology

Many predisposing factors

Cyclic nature of effects



Questions?