Metabolic Syndrome

Introduction to Metabolic Syndrome:

Describe what is meant by the term **'Metabolic Syndrome'**

- Metabolic syndrome is best defined as a cluster of risk factors that predispose individuals to type 2 diabetes and cardiovascular disease.
- With an annual incidence of MetSy thought to be 3% and more than 35% of Australian adults have metabolic syndrome (BHC).
- Studies show that more women than men in the same age groups tend to meet the criteria for metabolic syndrome, with prevalence increasing with age. Women aged 60-78 have a particularly high prevalence, with over a third affected. The risk increases as individuals grow older, especially among females.

Explain the **significance** of the overall **features of Metabolic Syndrome**

- Hypertension: arises from insulin resistance, endothelial dysfunction, and increased sympathetic nervous system activity = CV risk
- High triglycerides, low HDL cholesterol, small dense LDL particles: accelerates plaque formation = CV risk
    - Excess triglycerides can also accumulate in the pancreas, leading to pancreatitis
    - **Small, dense LDL** (often with high triglycerides) penetrate vessel walls more easily → ↑ atherosclerosis risk = **Apolipoprotein particle count** gives a better risk assessment than LDL concentration
- Insulin resistance/Raised fasting blood glucose levels: hyperinsulinemia (pancreas compensate) = β-cell exhaustion + insulin resistance, predisposing to T2DM.
    - Damages micro/macrovasculature → ↑ inflammation & oxidative stress
    - Complications: neuropathy, nephropathy, retinopathy, erectile dysfunction, poor wound healing, cognitive decline
    - Although 25% of insulin resistant patients have normal glucose tolerance
    - **High HbA1c** → poor glucose regulation → ↑ risk of stroke and myocardial infarction. Cardiovascular risk rises with hyperglycemia **even before diabetes develops**.
- Central obesity (excess fat around the abdomen): metabolically active, releasing free fatty acids, pro-inflammatory cytokines, and adipokines that promote insulin resistance = CV risk and T2D
    - Waist circumference increasingly preferred over BMI (e.g. Norway)
    - Highlights **visceral fat** as stronger risk factor than general obesity

Recognize the **clinical criteria** used to define Metabolic Syndrome and the **factors that make this complicated**

- Diagnosis requires meeting at least three out of these five criteria.
- Complicating factors:
    - **Different organisation** criterias: Mayo Clinic, American Heart Association, RACGP (Australian), and IDF
    - **Ethnic** differences: South Asians and Southeast Asians tend to have higher visceral fat at lower waist measurements
    - Overlap with related conditions: T2D, obesity, hypertension
    - Dynamic nature of risk: change numbers easily
    - **Fat distributions** (external SC vs internal visceral): visceral fat, also called hidden fat, surrounds internal organs and is linked to metabolic issues. It secretes less hormones like leptin, which helps regulate appetite. Visceral fat is associated with higher cortisol levels, which can influence stress and metabolic health. Individuals can be fat and fit or metabolically obese and thin outside, fat inside (TOFI). Visceral fat is associated with metabolic derangements – insulin resistance, high triglycerides, inflammation, altered cytokine levels.

	Mayo clinic	American Heart Association & NHLBI	RACGP	New IDF definition
Large waist	> 102cm in men > 89cm in women	> 102cm in men > 89cm in women	> 90-102cm in men > 80cm in women	Ethnic specific values
High triglyceride levels (or drug treatment)	> 1.7 mmol/L	> 1.7 mmol/L	> 1.7 mmol/L	> 1.7 mmol/L
Reduced HDL (or drug treatment)	< 1.04 mmol/L in men < 1.3 mmol/L in women	< 1.05 mmol/L in men < 1.3 mmol/L in women	< 1.0 mmol/L in men < 1.3 mmol/L in women	< 1.03 mmol/L in men < 1.29 mmol/L in women
Elevated blood pressure (or drug treatment)	> 130 systolic > 85 diastolic	> 130 systolic > 85 diastolic	> 130 systolic > 85 diastolic	> 130 systolic > 85 diastolic
Elevated fasting glucose (or drug treatment)	> 5.6 mmol/L	> 5.6 mmol/L	> 5.6 mmol/L	> 5.6 mmol/L

Describe the different **roles of plasma lipoproteins in lipid transport.** Rationalise the **'good' and 'bad' labels applied to cholesterol** in terms of lipid transport pathways and the specific roles of lipoprotein complexes

- Carry triglycerides (high energy), cholesterol, phospholipids in blood
- When food is ingested, dietary fats are emulsified by bile salts in the intestine, breaking them into smaller droplets. Lipases then digest triglycerides into their component parts. These are reassembled into triglycerides within intestinal mucosa and packaged into chylomicrons for transport.
- **Chylomicrons (dietary/exogenous pathway)**
    - Origin: intestine (after meals)
    - Cargo: dietary TG + cholesterol
    - Function: deliver TG → adipose (storage), muscle (energy)
- **VLDL (endogenous pathway)**
    - Origin: liver
    - Cargo: endogenous TG (made in liver)
    - Function: deliver TG → tissues; become IDL → LDL
- **LDL ("bad cholesterol")**
    - Origin: from IDL after TG removal
    - Cargo: cholesterol (esp. esters)
    - Function: deliver cholesterol → tissues (membranes, steroid hormones)
    - Clinical: excess LDL → arterial wall deposition → atherosclerosis
- **HDL ("good cholesterol")**
    - Origin: liver and intestine (nascent HDL)
    - Cargo: cholesterol collected from tissues
    - Function: reverse cholesterol transport → liver (excretion or transfer to LDL/VLDL via CETP)
    - Also donates ApoC-II & ApoE to other lipoproteins
    - Protective against CVD

Compare and contrast the roles of plasma lipoproteins in lipid transport, in the **endogenous, exogenous and reverse cholesterol transport pathways**

Exogenous Pathway (Dietary Lipids)

- **Lipoprotein:** Chylomicrone
- **Source:** Intestine (enterocytes, after meals)
- **Cargo:** Dietary TAGs, cholesterol, cholesterol esters
- **Role:**
    - Deliver TAGs → adipose (storage), muscle (energy), mammary gland (lactation)
    - After lipid delivery → chylomicron remnants → liver → degraded in lysosomes
- **Key point:** Handles exogenous (dietary) fat transport

Endogenous Pathway (Liver-Derived Lipids)

- Triggered when dietary intake of fatty acids, cholesterol, and carbohydrates (which can be converted to TAGs) is high.
- **Lipoprotein:** VLDL → IDL → LDL
- **Source:** Liver (esp. when intake of fatty acids, cholesterol, carbs is high)
- **Process:**
    - FFAs → TAGs; cholesterol → cholesterol esters → packaged into VLDL
    - **VLDL roles:**
        - High insulin → TAGs → adipose (storage)
        - Low insulin → TAGs mobilized → muscle (oxidation/energy)
    - TAG removal from VLDL → VLDL → IDL → LDL (cholesterol-rich)
- **LDL roles:**
    - Delivers cholesterol → tissues (muscle, adrenal, adipose)
    - Also to macrophages → foam cell formation → atherosclerosis risk
    - Excess LDL → liver (membrane synthesis, bile acids, cholesterol ester storage)
- **Clinical:** LDL = "bad cholesterol"

Reverse Cholesterol Transport (Protective Pathway)

- **Lipoprotein:** HDL
- **Source:** Liver & small intestine (nascent HDL)
- **Role:**
    - HDL acts as cholesterol scavenger → collects cholesterol from tissues, macrophages, foam cells
    - Returns cholesterol → liver (direct uptake or transfer to LDL/VLDL via CETP)
- **Clinical:** Protects against atherosclerosis → HDL = "good cholesterol"

Enterohepatic Pathway (Cholesterol Recycling)

- **Role of Liver:** Uses cholesterol to synthesize bile salts
- **Role in Transport:** Bile salts secreted into intestine → majority reabsorbed → returned to liver/gallbladder for reuse
- **Link:** Connects cholesterol metabolism with lipid digestion/absorption

Integrate the process of the **formation of atherosclerotic plaques** with lipoprotein and lipid transport

Cholesterol Background

- ~35 g cholesterol in 75 kg man (membranes, hormones, bile salts, vitamin D)
- Synthesized mainly by liver (~1 g/day, ~80% of body needs)
- Not present in plants → diet not essential for supply

Role of Lipoproteins in Atherosclerosis

- **LDL** (cholesterol-rich, from endogenous pathway) = main driver of atherogenesis
- High circulating LDL → cholesterol deposition in vessel wall
- **HDL** (reverse transport) → protective, removes cholesterol from tissues/plaques
- Dyslipidemia (↑LDL, ↓HDL) = major risk factor

Pathogenesis of Atherosclerosis

1. **Endothelial Injury/Dysfunction**
    - Causes: hypertension, smoking, diabetes, hyperlipidemia
    - Damaged endothelium → ↑permeability to LDL, expression of adhesion molecules
2. **LDL Entry & Modification**
    - LDL enters intima → becomes **oxidized/modified LDL**
    - Modified LDL is highly atherogenic
3. **Inflammatory Response**
    - Endothelial activation → attracts **monocytes & T-cells**
    - Monocytes migrate → intima → differentiate into macrophages
4. **Foam Cell Formation**
    - Macrophages engulf oxidized LDL via scavenger receptors
    - Cholesterol-laden macrophages = **foam cells**
    - Accumulation of foam cells → **fatty streaks** (earliest lesion)
5. **Plaque (Atheroma) Development**
    - Smooth muscle cells migrate into intima → secrete extracellular matrix → **fibrous cap** forms
    - Core of plaque = cholesterol + foam cells + necrotic debris
    - Results in arterial **narrowing & stiffening** → ↓blood flow
6. **Plaque Rupture & Thrombosis**
    - Thin/unstable fibrous cap may rupture
    - Foam cells release **tissue factor** → activates clotting cascade
    - Platelet aggregation + thrombus formation → possible **arterial occlusion**
    - Outcomes:
        - Coronary arteries → **myocardial infarction**
        - Cerebral arteries → **stroke**
        - Peripheral arteries → **peripheral arterial disease**

Extra Information

Cholesterol Synthesis & Inhibition

- Cholesterol mainly synthesized in body (~80%) from **acetyl-CoA**
- Rate-limiting enzyme: **HMG-CoA reductase**
- **Statins** = competitive inhibitors → ↓ cholesterol synthesis
- Normally feedback-regulated, but statins provide effective pharmacological control