

The Metabolic Syndrome

Chapter 420 | Part 12: Endocrinology and Metabolism

KEY CLINICAL POINTS

- 1 Metabolic syndrome is a constellation of metabolic abnormalities (central obesity, hypertriglyceridemia, low HDL-C, hypertension, and hyperglycemia) that increase the risk of cardiovascular disease (CVD) and diabetes mellitus.
- 2 Diagnosis requires meeting 3 out of 5 criteria based on either NCEP:ATPIII 2001 or Harmonizing Definition standards.
- 3 Waist circumference cutoffs for diagnosis vary by ethnicity in the Harmonizing Definition (e.g., ≥94 cm for men in Euroid/South African populations vs. ≥85 cm for Japanese men).
- 4 Weight reduction of at least 5% (preferably 10%) significantly improves insulin sensitivity and metabolic syndrome components.
- 5 Statin therapy is first-line for LDL reduction; high-intensity statins (Atorvastatin 40-80 mg, Rosuvastatin 20-40 mg) are indicated for LDL ≥190 mg/dL or for patients with diabetes aged 40-75 years.
- 6 GLP-1 receptor agonists (Semaglutide 2.4 mg, Liraglutide 3.0 mg) and Tirzepatide are approved for management of obesity and weight loss in metabolic syndrome.
- 7 Prevalence of metabolic syndrome in the U.S. is approximately 33.4%, with a significant increase with age (19.5% in ages 20-39 to 48.6% in ages ≥60).
- 8 Insulin resistance, driven by an overabundance of circulating free fatty acids (FFAs) from adipose tissue lipolysis, is the central unifying pathophysiology.
- 9 Patients with metabolic syndrome have a 1.5- to 3-fold increased risk for new-onset CVD and a 3- to 5-fold increased risk for type 2 diabetes.
- 10 Lipodystrophy (genetic or acquired) and certain antiretroviral therapies can cause severe insulin resistance mimicking the clinical presentation of metabolic syndrome.

DEFINITION & OVERVIEW

- **Definition:** Metabolic syndrome (syndrome X, insulin resistance syndrome) is a constellation of metabolic abnormalities that confer increased risk of cardiovascular disease (CVD) and diabetes mellitus.
- **Diagnostic Criteria:** Diagnosis requires fulfillment of 3 or more features based on either NCEP:ATPIII 2001 or Harmonizing Definition criteria.

Table 420-1: Comparison of Diagnostic Criteria

Criterion	NCEP:ATPIII 2001 Threshold	Harmonizing Definition Threshold
Central Obesity (Waist)	>102 cm (males), >88 cm (females)	Men: ≥94 cm (Euroid, Sub-Saharan African, Eastern/Middle Eastern); ≥90 cm (South Asian, Chinese, South/Central American); ≥85 cm (Japanese)

(Japanese). Women: ≥ 80 cm (Europid, Sub-Saharan African, Eastern/Middle Eastern); ≥ 80 cm (South Asian, Chinese, South/Central American); ≥ 90 cm (Japanese). |

| **Hypertriglyceridemia** | ≥ 150 mg/dL or specific medication | > 150 mg/dL or specific medication |

| **Low HDL-C** | < 40 mg/dL (males), < 50 mg/dL (females) or specific medication | < 40 mg/dL (males), < 50 mg/dL (females) or specific medication |

| **Hypertension** | ≥ 130 mmHg systolic or ≥ 85 mmHg diastolic or specific medication or previously diagnosed T2DM | > 130 mm systolic or > 85 mm diastolic or previous diagnosis or specific medication |

| **Fasting Glucose** | ≥ 100 mg/dL or specific medication or previously diagnosed T2DM | ≥ 100 mg/dL (alternative: drug treatment of elevated glucose levels) |

Evolution of Criteria

- **Core Features:** Central obesity, hypertriglyceridemia, low HDL-C, hyperglycemia, and hypertension.
- **Clinical Basis:** The evolution of these criteria reflects growing evidence regarding the link between these specific metabolic factors and cardiovascular risk.

Global Health & Epidemiology

- **U.S. Prevalence:** 33.4% in adults (NHANES 1999-2018).
- **Age Correlation:**
 - 20-39 years: 19.5%
 - ≥ 60 years: 48.6%
- **Trend:** Prevalence is age-dependent, with a noted reduction after age 80 across all subgroups.

ETIOLOGY & PATHOPHYSIOLOGY

- **Central Mechanism:** Insulin resistance (IR) caused by systemic defects in insulin action.
- **Progression:** Postprandial hyperinsulinemia → fasting hyperinsulinemia → hyperglycemia.

Insulin Resistance Mechanisms

- **Free Fatty Acids (FFAs):** Primary driver of IR.
 - Source: Released from adipose-tissue triglyceride stores via lipolysis.
 - Impact on Liver: Increased FFA flux → increased VLDL production, triglyceride accumulation, and enhanced glucose production.
 - Impact on Muscle: FFAs impair insulin-mediated glucose uptake and increase triglyceride accumulation.
- **Lipolysis Sensitivity:** Inhibition of lipolysis in adipose tissue is the most sensitive pathway of insulin action; its failure leads to a cycle of increasing FFAs and worsening IR.

Cardiovascular Disease Risk

- **Mortality:** Patients with metabolic syndrome are 2x more likely to die from CVD.
 - Acute events: 3x higher risk for myocardial infarction or stroke.
- **Prevalence in CHD:** Up to 60% in patients > 75 years; $\approx 35\%$ in premature CAD (age ≤ 45).
 - Higher prevalence noted specifically in women.

Dyslipidemia

- **VLDL & Triglycerides:** FFA flux to liver → increased production of apoB-containing, triglyceride-rich VLDLs.
- **Apolipoprotein C-III:** Increased levels on VLDLs inhibit lipoprotein lipase → reduced clearance of TG-rich remnants → higher risk for ASCVD.
- **HDL Cholesterol:** Reduced due to altered composition (lower cholesterol content) and increased clearance from circulation.
 - Mechanism: Cholesteryl ester transfer protein-mediated alterations in triglycerides make the HDL particle small and dense.
- **LDL Composition:** When fasting serum triglycerides are >2.0 mM (≈180 mg/dL), there is a predominance of small dense LDLs, which are more atherogenic.

Hypertension Mechanisms

- **Insulin Paradox:** Normal insulin → nitric oxide → vasodilation. In IR: Vasodilatory effect lost, but renal sodium reabsorption is preserved.
 - Ethnicity Note: Sodium reabsorption increased in Caucasians; not observed in Africans or Asians.
- **Sympathetic Nervous System (SNS):** Insulin increases SNS activity; this effect is preserved in the setting of insulin resistance.
- **Endothelial Dysfunction:** Impaired PI3K signaling → imbalance between nitric oxide and endothelin 1 → decreased blood flow.
- **Angiotensin II:** Increased angiotensinogen expression in adipose tissue → increased circulating Angiotensin II → vasoconstriction.
- **Perivascular Adipose Tissue:** Release of reactive oxygen species (ROS) from NADPH oxidase → impaired endothelial function and local vasoconstriction.

Proinflammatory Cytokines

- **Source:** Overproduction by expanded adipose tissue mass; primary source is adipose tissue-derived macrophages.
 - Key Mediators: IL-1, 6, 18; resistin; TNF- α ; and C-reactive protein (CRP).
 - Impact: These cytokines contribute to insulin resistance and promote a pro-thrombotic state.

Other Etiologic Factors

- **Lipodystrophy:** Both genetic (e.g., Berardinelli-Seip, Dunnigan) and acquired (e.g., HIV-related or from certain antiretroviral therapies) can cause severe insulin resistance and metabolic syndrome components.

CLINICAL FEATURES

- **Symptoms:** Typically asymptomatic.
- **Physical Examination:**
 - Common: Elevated waist circumference and blood pressure.
 - Rare (Severe IR indicators): Lipodystrophy or acanthosis nigricans.

Associated Diseases

- **CVD Risk:** 1.5- to 3-fold risk for new-onset CVD in non-diabetic patients.
 - Study (INTERHEART): Diabetes (OR 2.72) and hypertension (OR 2.60) are stronger predictors than other factors.

- **Other Risks:** Increased risk of stroke, peripheral vascular disease, and Alzheimer's disease.
 - **Mortality Correlation:** In the REGARDS study, metabolic syndrome + high hsCRP → 1.34 relative risk for all-cause mortality (higher in whites than blacks).
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DIFFERENTIAL DIAGNOSIS

- **Clinical Context:** History must include screening for obstructive sleep apnea and polycystic ovary syndrome (PCOS) in premenopausal women.
 - Family history: Used to determine risk for CVD and diabetes.
 - **Distinguishing Features:**
 - Normal weight individuals may still be insulin-resistant (common in India, SE Asia, Central America).
 - Lipodystrophic disorders (genetic or acquired) should be considered as causes of severe insulin resistance mimicking metabolic syndrome.
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INVESTIGATIONS & DIAGNOSIS

- **Laboratory Tests:**
 1. Fasting lipids and glucose.
 2. Biomarkers: apoB, hsCRP, fibrinogen, uric acid, urinary albumin/creatinine ratio, and liver function.
 3. Specific tests: Sleep study for OSA; testosterone, LH, and FSH for suspected PCOS.
 4. MAFLD assessment: FIB4 score or elastography.
 - **Diagnostic Algorithm:**
 1. Measure waist circumference and blood pressure at the bedside.
 2. Obtain fasting lipids and glucose in the laboratory.
 3. Assess for presence of ≥ 3 criteria (NCEP:ATPIII or Harmonizing Definition).
 4. If criteria met, evaluate for associated conditions (CVD, T2DM, Sleep Apnea, PCOS, MAFLD).
 5. Consider imaging (DEXA, CT, MRI) if fat distribution needs differentiation.
 6. Consider sleep study if symptoms of obstructive apnea are present.
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MANAGEMENT & TREATMENT

1. **Weight Management:** Identify obesity as the primary driver; target weight reduction $\geq 5\%$ (preferably 10%) to improve insulin sensitivity.
 2. **Statin Therapy:** First-line for LDL reduction.
 - High-intensity statins (Atorvastatin 40–80 mg, Rosuvastatin 20–40 mg) for LDL ≥ 190 mg/dL or patients with diabetes aged 40–75 years.
 3. **GLP-1 Receptor Agonists:** Semaglutide (2.4 mg), Liraglutide (3.0 mg).
 4. **Tirzepatide:** Approved for obesity and weight loss in metabolic syndrome.
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KEY PEARLS & HIGH-YIELD POINTS

- **Core Definition:** Metabolic syndrome is a cluster of conditions (obesity, high TG, low HDL, hypertension, hyperglycemia) that significantly increases CVD and T2DM risk.

- **Diagnostic Thresholds:** Requires 3 of 5 criteria; note the ethnicity-specific waist circumference cutoffs in the Harmonizing definition.
- **Pathophysiology:** Insulin resistance is driven by excess FFAs from adipose tissue, leading to a pro-inflammatory state (IL-6, TNF- α) and a pro-thrombotic state (PAI-1, fibrinogen).
- **Dyslipidemia Profile:** Characterized by high triglycerides, low HDL, and atherogenic small dense LDL.
- **Weight Loss Goal:** A reduction of $\geq 5\%$ is the primary intervention to improve insulin sensitivity.
- **Clinical Screening:** Always screen for obstructive sleep apnea (OSA) and polycystic ovary syndrome (PCOS) in relevant patients.

REFERENCE TABLES

TABLE 420-1

NCEP:ATPIII a 2001 and Harmonizing Definition Criteria for the Metabolic Syndrome NCEP:ATPIII 2001 Three or more of the...

NCEP:ATPIII 2001	HARMONIZING DEFINITION ^b		
Three or more of the following: • Central obesity: waist circumference >102 cm (males), >88 cm (females) • Hypertriglyceridemia: triglyceride level ≥ 150 mg/dL or specific medication • Low HDLc cholesterol: <40 mg/dL and <50 mg/dL for men and women, respectively, or specific medication • Hypertension: blood pressure ≥ 130 mmHg systolic or ≥ 85 mmHg diastolic or specific medication • Fasting plasma glucose level ≥ 100 mg/dL or specific medication or previously diagnosed type 2 diabetes	Three of the following: Waist circumference (cm)		
	Men	Women	Ethnicity
	≥ 94	≥ 80	Europid, sub-Saharan African, Eastern and Middle Eastern
	≥ 90	≥ 80	South Asian, Chinese, and ethnic South and Central American
	≥ 85	≥ 90	Japanese

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- Fasting triglyceride level >150 mg/dL or specific medication
 - HDL cholesterol level <40 mg/dL and <50 mg/dL for men and women, respectively, or specific medication
 - Blood pressure >130 mm systolic or >85 mm diastolic or previous diagnosis or specific medication
 - Fasting plasma glucose level ≥ 100 mg/dL (alternative indication: drug treatment of elevated glucose levels)