Metabolic Syndrome (Insulin Resistance Syndrome)

- People with metabolic syndrome are at increased risk of coronary heart disease and other diseases related to plaque deposits/buildups in artery walls (stroke and peripheral vascular disease) and type 2 diabetes mellitus.
- Underlying risk factors for this syndrome are abdominal obesity and insulin resistance.
- Criteria for diagnosis of metabolic syndrome are based on common clinical measures including waist circumference, triglycerides, HDL-C, blood pressure, and fasting glucose levels. The presence of defined abnormalities in any three of these five measures constitutes a diagnosis of metabolic syndrome.

What is metabolic syndrome?

Metabolic syndrome is characterized by a group of metabolic risk factors in an individual, which include abdominal obesity, atherogenic dyslipidemia, elevated blood pressure, insulin resistance or glucose intolerance, prothrombotic state (as evidenced by high fibrinogen or plasminogen activator inhibitor-1 in the blood), and proinflammatory state with elevated C-reactive protein in the blood.

What is the main reason for an increased number of patients with metabolic syndrome?

The National Cholesterol Education Program's Adult Treatment Panel III report (ATP III) considers the rising obesity epidemic in the United States to be responsible for the increasing prevalence of metabolic syndrome. Risk factors associated with obesity increase proportionately as abdominal girth expands, causing elevation of serum cholesterol, low HDL cholesterol, hyperglycemia, and hypertension. Other factors, such as aging, physical inactivity, proinflammatory state, hormonal changes/imbalances, and genetic predisposition have been implicated as contributors as well.

What are the major components of metabolic syndrome?

The National Cholesterol Education Program identifies metabolic syndrome as a multiplex risk factor for cardiovascular disease. Although criteria established by ATP III differ slightly from other organizations, all recognize CVD as a primary outcome of metabolic syndrome. World Health Organization (WHO) agrees that CVD is a risk factor associated with metabolic syndrome, but posits that insulin resistance is a required component for diagnosis. The American Association of Clinical Endocrinologists (AACE) proposes a third set of clinical criteria for insulin resistance syndrome and parallel those of WHO and ATP III, but do not define a specific number of risk factors. ATP III considers the six following components to be characteristic of metabolic syndrome:

1. *Abdominal obesity* is the form of obesity most often associated with metabolic syndrome. It presents clinically as increased waist circumference greater than 40 inches in men and 35 inches in females.

2. *Atherogenic dyslipidemia* is evidenced by raised triglycerides and low concentrations of HDL cholesterol on lipid profile studies. Other lipid abnormalities may also be noted with elevated LDL and small HDL particles.

3. *Elevated blood pressure* is associated with obesity and insulin-resistance as increasing arterial stiffness contributes significantly to systolic hypertension in the elderly.

4. *Insulin resistance* is present in the majority of people with metabolic syndrome and is strongly linked to CVD. Patients with longstanding insulin resistance often show symptoms of *glucose intolerance*, and if left untreated will evolve into full-blown type 2 diabetes.

5. *A proinflammatory state* manifests itself through elevations of highly sensitive C-reactive protein (hs-CRP). As a result of obesity, excess adipose tissue releases inflammatory cytokines that may be reflected in elevated hs-CRP levels. Prospective studies (Aguilar et al, 2006) in middle-aged individuals have observed that increased serum CRP levels may predict the development of metabolic syndrome.

6. *A prothrombotic state* is characterized by increased plasma plasminogen activator inhibitor (PAI)-1 and fibrinogen in metabolic syndrome. Fibrinogen is an acute-phase reactant (like CRP) and rises in response to a high-cytokine state. Prothrombotic and proinflammatory states may be metabolically interconnected.

What are the criteria for diagnosis of metabolic syndrome?

The National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) proposed a simple set of diagnostic criteria based on common clinical measures including waist circumference, triglycerides, HDL-C, blood pressure, and fasting glucose level.

The presence of defined abnormalities in any three of these five measures constitutes a diagnosis of metabolic syndrome. Patients having fewer than three abnormalities are at high-risk for developing metabolic syndrome and type 2 diabetes mellitus, and require close monitoring and ongoing assessment.

Please refer to Table 1 on the following page for diagnostic criteria for Metabolic Syndrome.

Table 1: Diagnostic Criteria for Metabolic Syndrome (Adapted from AHA, 2004)

Measure (Any 3 of 5 Criteria Constitute Diagnosis of Metabolic Syndrome)	**Categorical Cut Points**
Elevated waist circumference* + **To measure waist circumference, locate top of right iliac crest. Place a measuring tape in a horizontal plane around the abdomen at level of iliac crest. Before reading tape measure, ensure the tape is snug but does not compress the skin and is parallel to floor. Measurement is made at the end of normal expiration.*	≥ 102 cm (≥ 40 inches) in men ≥ 88 cm (≥ 35 inches) in women *+Some US adults of non-Asian origin (e.g. white, black, Hispanic) with marginally increased waist circumference (e.g. 94-101 cm or 37-39 inches in men; and 80-87 cm or 31-34 inches in women) may have strong genetic contribution to insulin resistance and should benefit from changes in lifestyle habits, similar to men with categorical increases in waist circumference. Lower waist circumference cut point (e.g. ≥ 90 cm/35 inches in men; and ≥ 80 cm/31 inches in women) appears to be appropriate for Asian Americans.*
Elevated Triglyceride *#Fibrates and nicotinic acid are the most commonly used drugs for elevated Triglyceride and reduced HDL-C. Patients taking one of these drugs are presumed to have high triglyceride and low HDL.*	≥ 150 mg/L (1.7 mmol/L) or Drug treatment for elevated triglyceride
Reduced HDL-C	< 40 mg/dL (1.03 mmol/L) in men < 50 mg/dL (1.3 mmol/L) in women or Drug treatment for reduced HDL-C
Elevated BP	≥ 130 mm Hg systolic BP, or ≥ 85 mm Hg diastolic BP, or Drug treatment for hypertension
Elevated fasting glucose	≥ 100 mg/dL or drug treatment for elevated glucose

What is the primary goal of clinical management of metabolic syndrome?

The primary goal of clinical management of metabolic syndrome is to reduce the risk for clinical atherosclerotic disease. A second closely related goal is to reduce the risk for type 2 diabetes mellitus in patients who are at high-risk. First line therapy is to reduce major modifiable risk factors such as cessation of tobacco use, target lowering LDL-C and triglycerides, raise HDL, and lower blood pressure and glucose levels to recommended goals. Both the long-term and short-term goals include interventions to reduce metabolic risk factors and include weight loss, increased physical activity, and diet modification to low fat intake. Refer to the section on medical nutrition therapy for additional information (pages 103-105).

Blood pressure management including lifestyle changes are recommended for readings that range from 120 to 139 systolic and 80 to 90 mmHg diastolic. Readings higher than ≥ 140/90 should be considered for drug therapies according to current hypertension guidelines. When either diabetes or chronic renal disease is present, reducing blood pressure to < 120/80 mm Hg, with drugs if necessary, is recommended.

Table 2: Medication Therapy

Action of Drug	Drug Choices Commonly Used
ATHEROGENIC DYSLIPIDEMIA **Standard LDL-Lowering Drugs** Medication therapy for the treatment of atherogenic dyslipidemia is based on NCEP guidelines and target lowering the LDL-C and raising HDL-C.	Statins, exetimibe, and bile acid sequestrants (Recent research findings from the parent company Merck/Schering-Plough (2008) question the efficacy of exetimibe when combined with simvastatin (Vytorin)).
Secondary Drugs Produce moderate reductions of LDL-C	Nicotinic acid and fibrates are considered to be secondary drugs to lower non-HDL-C and to raise HDL-C after LDL-C goals are achieved.
Severe Hypertriglyceridemia	The fibrates or nicotinic acid are first-line therapy for patients with severe hypertriglyceridemia for the purpose of preventing acute pancreatitis. **CAUTION:** Caution must be exercised in using fibrates (particularly gemfibrozil) with statins because of the accentuated risk for severe myopathy.
Low Dose Aspirin	Use of low-dose aspirin is recommended for individuals exhibiting the following: 1) prothrombotic states characterized by elevation of plasminogen activator inhibitor-1 and fibrinogen; 2) a 10-year risk for CHD $\geq$ 10%; 3) those with overt type 2 diabetes; 4) ASCVD; or 5) other high risk categories In patients with ASCVD in whom aspirin is contraindicated, consideration should be given to use of clopidogrel.
Treatment of IFG	Drug therapy to reduce plasma glucose or insulin resistance is not recommended for patients with IFG. Once diabetes is diagnosed, drug therapy is indicated to achieve the recommended ADA goal for hemoglobin A1C of < 7% (6.5% per AACE).

What are the therapeutic goals for long-term prevention of ASCVD?

Refer to Table 3 for current therapeutic goals for the long-term prevention of ASCVD.

Table 3: Therapeutic Goals for ASCVD Prevention

Therapeutic Target	Goals of Therapy	Therapeutic Recommendations
Abdominal obesity	❖ Reduce body weight by 7%-10% during first year of therapy ❖ Continue weight loss thereafter to extent possible with goal to ultimately achieve desirable weight (BMI < 25 kg/m2)	Consistently encourage weight maintenance/ reduction through appropriate balance of physical activity, caloric intake, and formal behavioral programs when indicated to maintain/achieve waist circumference of < 40 inches in men and < 35 inches in women. Aim initially at slow reduction of and 7%-10% from baseline weight. Even small amounts of weight loss are associated with significant health benefits.
Physical inactivity	❖ Regular moderate-intensity physical activity; at least 30 minutes of continuous/intermittent (preferably 60 minutes) 5 days/week, but preferably daily	In patients with established CVD, assess risk with detailed physical activity history and/or exercise test to guide prescription. Encourage 30 to 60 min of moderate-intensity aerobic activity (e.g., brisk walking), preferably daily, supplemented by an increase in daily lifestyle activities (e.g. pedometer step tracking, walking breaks at work, gardening, household work). Higher exercise times achieved by accumulating exercise throughout day. Encourage resistance training 2 d/wk. Advise medically supervised programs for high-risk patients (e.g. recent acute coronary syndrome or revascularization, CHF).
Atherogenic diet	❖ Reduced intakes of saturated fat, transfat, cholesterol	Saturated fat < 7% of total calories; reduce trans fat; dietary cholesterol < 200 mg/d; total fat 25%-35% of total calories. Most dietary fat should be unsaturated, simple sugars should be limited**.**

References:

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