MISSOURI DUReport

Metabolic Syndrome

Refer to Appendix A for quick reference on diagnosis and treatment guidelines

Introduction

Metabolic syndrome, also known as “Syndrome X” or the “insulin resistance syndrome”, is present in approximately 25% of the overall U.S. population. Prevalence increases with increasing body fat, particularly abdominal fat; a key contributor to physiological disturbances making up this syndrome. Approximately 60% of obese U.S. males (defined as a body mass index [BMI] ≥ 30 kg/m2) and 50% of obese U.S. females have metabolic syndrome, with most affected patients undiagnosed. Metabolic syndrome encompasses a set of metabolic risk factors that increase risks for cardiovascular disease morbidity and mortality. Recent evidence also indicates that metabolic syndrome substantially increases risk of developing type 2 diabetes mellitus, with risk for both diseases increasing with number of metabolic risk factors involved.

Broadly defined, metabolic syndrome includes changes in glucose, lipid and uric acid metabolism leading to key changes in glucose tolerance and dyslipidemia, hemodynamic changes leading to hypertension, and other changes leading to a pro-inflammatory and pro-thrombotic condition. Metabolic syndrome is operationally defined by the US Public Health Service in the Adult Treatment Panel III (ATP III) guidelines, focusing on the key metabolic risk factors of *abdominal obesity, elevated triglycerides, a low HDL level, increased blood glucose and high blood pressure.*

The ATP III treatment recommendations place a primary emphasis on therapeutic lifestyle changes, which include weight loss, increased physical activity, and diet modification. ATP III guidelines also suggest that established coronary risk factors such as dyslipidemia, hyperglycemia, hypertension, and the prothrombotic state be treated pharmacologically to reduce risks of coronary heart disease.

Background

Metabolic syndrome is closely linked to a generalized metabolic condition called *insulin resistance* in which normal tissue sensitivity to actions of insulin are impaired. Excess body fat (particularly abdominal obesity) and physical inactivity are key factors that promote insulin resistance development. Some individuals are also genetically predisposed to insulin resistance. Contributing factors of metabolic syndrome are obesity, physical inactivity, familial hypercholesterolemia, insulin-resistance, and other genetic factors.

Diagnosis

The ATP III identifies metabolic syndrome as a set of ≥3 of the risk factors identified in Table 1.

Table 1: ATP III Identification of the Metabolic Syndrome

Metabolic Risk Factor*	Defining Level
Abdominal Obesity	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 mmHg
Fasting glucose	≥110 mg/dL

** The ATP III panel found no evidence to support a recommendation of routine screening for insulin-resistance, a pro-inflammatory state, or a prothrombotic state for the diagnosis of the metabolic syndrome.*

†*Some men may develop multiple metabolic risk factors when a waist circumference is only marginally increased, e.g., 94-102 cm (37-39 in).*

Clinical Management:

- Treat underlying causes of overweight and obesity.
- Treat lipid and non-lipid risk factors if they persist despite therapeutic lifestyle changes.

- **Treatment of underlying causes: Therapeutic Lifestyle Changes (TLC)**

  - **Diet modification**
    - Low-calorie diet (800-1500 kcal/day)
    - Total fat ≤30% of total calories, saturated fat <10% of calories, cholesterol <300 mg/day
    - Refer to the *NHLBI Obesity Education Initiative* available online at www.nhlbi.nih.gov/guidelines/obesity.

  - **Weight control**
    - **Reduce body weight by 10% in 6 months of therapy.** In ATP III, being overweight or obese is recognized as a major, underlying risk factor for CHD and is identified as a direct intervention target. Overweight is defined as "a body mass index (BMI) of 25 to 29.9 kg/m^2" and obesity as "a BMI of ≥ 30 kg/m^2." Weight reduction will enhance LDL-lowering and reduce all risk factors of metabolic syndrome. Recommended approaches for treating overweight and obesity are in the clinical guidelines of the *NHLBI Obesity Education Initiative.*

  - **Physical activity**
    - **At least 30 minutes of aerobic exercise most days of the week.** Physical inactivity, which intensifies lipid and non-lipid risk factors of metabolic syndrome, is an additional major underlying risk factor for CHD. A lack of physical activity may further enhance risk by impairing cardiovascular fitness and coronary blood flow. Regular physical activity reduces VLDL levels, raises HDL cholesterol, and in some persons, lowers LDL levels. It also can lower blood pressure, reduce insulin resistance, and improve cardiovascular function. Thus, the ATP III recommends that regular physical activity become a routine component in management of high serum cholesterol. The evidence for this recommendation may be viewed in the *U.S. Surgeon General's Report on Physical Activity* available online at www.cdc.gov/nccdphp/sgr/sgr.htm.

Pharmacologic treatment:

- **Elevated LDL (≥100 mg/dL):**
  - **Lower LDL below goal of <100 mg/dL with TLC and initiation of a LDL-lowering medication as needed.** The ATP III continues to identify elevated LDL as the primary target of cholesterol-lowering therapy. Refer to the *Oct/Nov 2003 Missouri DUR Report on Statin Therap*y available online at www.heritage-info.com/mocaidrx/.

- **Elevated triglycerides (>150mg/dL):**
  - **Lower triglycerides ≤150 mg/dL with TLC and intensify therapy with LDL-lowering medication.**

Table 2: ATP III Classification of Serum Triglycerides (mg/dL)

Triglyceride Category	ATP III levels
Normal	**< 150**
Borderline high	**150-199**
High	**200-499**
Very high	**≥500**

  - If triglycerides remain 200-499 mg/dL after LDL goal is attained, intensify therapy with an LDL-lowering drug or add nicotinic acid or fibrate to further lower VLDL.
  - If triglycerides are ≥500 mg/dL, target triglycerides by initiating a very low-fat diet (≤15% of calories from fat), weight management, physical activity, and add fibrate or nicotinic acid.

- **Low HDL cholesterol (<40 mg/dL):**
  - **Increase HDL ≥40 mg/dL after first reaching LDL goal <100 mg/dL by intensifying weight management and increasing physical activity.** If triglycerides 200-499 mg/dL, achieve non-HDL goal. If triglycerides <200 mg/dL (isolated low HDL) in CHD or a CHD risk equivalent, consider nicotinic acid or fibrate.
  - CHD risk equivalents include diabetes mellitus, peripheral arterial disease, abdominal aortic aneurysm, symptomatic carotid artery disease, renal artery disease, or the presence of multiple CHD risk factors that together confer a 10-year risk for coronary events >20%.

- **Hypertension (>140/90 mmHg):**

    - **Goal BP is ≤140/90 mmHg.** Thiazide-type diuretics as initial therapy for most patients with hypertension, either alone or in combination with one of the other classes (ACEIs, ARBs, BBs, CCBs) demonstrated to be most beneficial in randomized clinical trials.
    - **If patient presents with diabetes, goal BP is <130/80 mmHg.** In patients with diabetes, a combination of 2 or more drugs is usually needed to achieve the target BP. Addition of ACE inhibitors or ARBs reduce the progression of diabetic nephropathy and reduce albuminuria.
    - Refer to "The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report" for all oral antihypertensive drugs and the treatment guidelines of patients with compelling indications, available online at www.nhlbi.nih.gov/guidelines/hypertension.

- **Prothrombotic state:**

    - **Use 81 mg aspirin daily for CHD patients to reduce prothrombotic state.** The American Heart Association states "studies show aspirin helps prevent the occurrence of MI, hospitalization for recurrent angina, and strokes from occurring in people at high risk." Use of aspirin reduces the incidence of MI and has a neutral effect on cerebrovascular events in healthy males >45 years of age, males with an increased cardiovascular risk profile, and persons with diabetes mellitus or hypertension.

References

1. "Expert Panel on the Identification and Treatment of Overweight and Obesity in Adults." *Arch. Intern. Med.* 1998; 158: 1855-67.
2. Ford ES, Giles WH, Dietz WH. "Prevalence of the metabolic syndrome among US adults: findings from the Third National Health and Nutrition Examination Study." *J. Am. Med. Assoc.* 2002; 287: 356-9.
3. "The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III)." *Circulation* 2002; 106: 3143-3421.
4. "The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report." *JAMA* 2003; 289(19):2560-7.
5. Wagh A, Stone N. "Treatment of metabolic syndrome." Expert Review of Cardiovascular Therapy 2004; 2(2): 213-28.

Appendix A Metabolic Syndrome Quick Reference

Diagnosis: The ATP III identifies the metabolic syndrome as ≥3 risk factors identified in Table 1.

Table 1: ATP III Identification of the Metabolic Syndrome

Metabolic Risk Factor*	Defining Level
Abdominal Obesity Men† Women	Waist Circumference >102 cm (>40 in) >88 cm (>35 in)
Triglycerides	≥150 mg/dL
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** The ATP III panel found no evidence to support a recommendation of routine screening for insulin-resistance, a proinflammatory state, or a prothrombotic state for the diagnosis of the metabolic syndrome.*

†*Some men may develop multiple metabolic risk factors when a waist circumference is only marginally increased, e.g., 94-102 cm (37-39 in).*

Treatment:

- **Therapeutic Lifestyle Changes**
  - Diet modification: Low-calorie diet (800-1500 kcal/day)
  - Reduce body weight by 10% in 6 months of therapy.
  - At least 30 minutes of aerobic exercise most days of the week.

- **Pharmacologic Treatment**
  - Lower LDL below goal of <100 mg/dL with TLC and initiation of a LDL-lowering medication as needed.
  - Increase HDL ≥40 mg/dL after first reaching LDL goal <100 mg/dL by intensifying weight management and increasing physical activity.
  - Lower triglycerides ≤150 mg/dL with TLC and intensify therapy with LDL-lowering medication.
  - Goal BP is ≤140/90 mmHg. If patient presents with diabetes, goal BP is <130/80 mmHg.
  - Use 81 mg aspirin daily for CHD patients to reduce prothrombotic state.

Quick References to Treatment Guidelines:

- ATP III (Cholesterol-reduction): www.nhlbi.nih.gov/guidelines/cholesterol
- JNC 7 (B/P reduction): www.nhlbi.nih.gov/guidelines/hypertension
- NHLBI Obesity Education Initiative: www.nhlbi.nih.gov/guidelines/obesity
- U.S. Surgeon General's Report on Physical Activity: www.cdc.gov/nccdphp/sgr/sgr.htm
- Oct/Nov 2003 Missouri DUR Report on Statin Therapy: www.heritage-info.com/mocaidrx/

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