Metabolic Syndrome: A Growing Epidemic

Faculty
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Faculty Disclosure
Contributing faculty, John J. Whyte, MD, MPH, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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Division Planner Disclosure
The division planner has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Audience
This course is designed for certified surgical technicians and assistants involved in the care of adults or adolescent patients who exhibit risk factors for metabolic syndrome.

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A complete Works Cited list begins on page 25.

Disclosure Statement

It is the policy of CME Resource not to accept commercial support.

Course Objective

As metabolic syndrome continues to become a more prevalent problem in the United States, healthcare professionals will encounter patients with this constellation of symptoms on a more frequent basis. The purpose of this course is to educate surgical professionals about the epidemiology and treatment of metabolic syndrome.

Learning Objectives

Upon completion of this course, you should be able to:

1. Define metabolic syndrome.
2. Discuss the epidemiology of metabolic syndrome in the U.S., based on age, sex, race, and other factors.
3. Describe the risk factors of metabolic syndrome.
4. Define the screening tools used to diagnose metabolic syndrome.
5. Describe the current dietary recommendations.
6. Describe the current physical activity recommendations.
7. Describe pharmaceutical interventions currently available for obesity.
8. Review the circumstances when surgery should be considered as a treatment option for obesity.
9. Define dyslipidemia and its treatment recommendations.
10. Review hypertension and its treatment modalities.

EB EVIDENCE-BASED PRACTICE RECOMMENDATION

Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the course material for better application to your daily practice.

INTRODUCTION

Metabolic syndrome, a constellation of conditions and/or risk factors, leads to an increased incidence of cardiovascular (CV) disease as well as type 2 diabetes mellitus. It was first described in 1988 and has been referred to by a variety of names, including "Reaven's syndrome," "deadly quartet," "syndrome X," "insulin resistance syndrome," and "dysmetabolic syndrome" [1]. In general, the components include central adiposity, hypertension, dyslipidemia, insulin resistance, and a proinflammatory state. Each component is independently associated with an increased cardiovascular risk and diabetic risk. As a composite, metabolic syndrome is a strong predictor of diabetes and can serve as an adjunct to other measures of the risk of cardiovascular events. Aggressive treatment of metabolic syndrome components with lifestyle modifications and/or pharmacotherapy is necessary to reduce morbidity and mortality.

In the last several years, the usefulness of the term "metabolic syndrome" has been questioned by some experts and organizations, including the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) [127]. Concerns raised include the use of varying definitions, uncertainty about appropriate cutpoints, the inclusion of different phenotypes, and lack of clarity regarding pathogenesis. The ADA has urged additional research to determine the significance of the clustering of cardiometabolic risk factors. The authors of the ADA/EASD appraisal do comment that the concept of a "syndrome" may encourage diagnosis and treatment of the multiple components when one is observed [127]. The American Heart Association (AHA), in their 2005 statement on the diagnosis and management of the metabolic syndrome, notes that there may not be a single underlying cause but that the construct remains useful to identify people at increased risk of atherosclerotic cardiovascular disease [88].

The following case study will be referenced throughout the text to illustrate the challenges of diagnosing and treating patients with metabolic syndrome:

Mr. G *is a white male, 54 years of age, with a past medical history of hypertension. At his yearly physical, he reports that he is doing well overall, with no complaints other than some dyspnea on exertion, which has been long-standing. Current medications include a thiazide diuretic and aspirin. He works as an accountant and does not get much physical activity during the day.*

DEFINITION OF METABOLIC SYNDROME

NATIONAL CHOLESTEROL EDUCATION PROGRAM ADULT TREATMENT PANEL

There are several diagnostic definitions for metabolic syndrome. In 2001, the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III proposed diagnostic criteria for metabolic syndrome ***(Table 1)*** [2]. In 2004, this definition was updated, resulting in a modification of the glucose criterion. Approximately one year after the ATP III report, a panel consisting of representatives from the AHA, National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (NIH), and the ADA reviewed additional studies that were not available at the time of the ATP III report [3]. In this review, they determined that lowering the glucose cutoff more effectively identified men at high risk of diabetes and coronary artery disease. Therefore, the panel implemented a new ADA cutoff for impaired fasting glucose (IFG), specifically an IFG of greater than 100 mg/dL. Although identification of impaired glucose tolerance (IGT) was not included in the criteria, the panel noted that there may be value in incorporating this test for patients with metabolic syndrome or with 2 or more risk factors.

NCEP ATP III CLINICAL IDENTIFICATION OF THE METABOLIC SYNDROME*

Risk Factor	Defining Level
Abdominal obesity (waist circumference)	Men: >102 cm (>40 in) Women: >88 cm (>35 in)
Triglycerides	≥150 mg/dL
High-density lipoprotein cholesterol	Men: <40 mg/dL Women: <50 mg/dL
Blood pressure	≥130/≥85 mm Hg
Fasting glucose	≥100 mg/dL

*Defined by the presence of three or more of the listed components

Source: [2; 3] *Table 1*

An oral glucose tolerance test could help to classify patients who do not have IFG, diagnose diabetes in patients who do have IFG, and alert clinicians to increased diabetes risk [3].

In addition, as part of metabolic syndrome, the following conditions may be present:

- Inflammation—increases in acute phase reactants such as C-reactive protein, cytokines, and adhesion molecules
- Prothrombosis—increases in plasminogen activator inhibitor, d-dimers, and fibrinogen
- Oxidant stress—increases in conjugated dienes and lipid peroxides
- Endothelial dysfunction

As defined by the NCEP ATP III, metabolic syndrome is not the same as insulin resistance syndrome, although insulin resistance is common in patients with metabolic syndrome.

THE WORLD HEALTH ORGANIZATION

The World Health Organization (WHO) also has developed criteria for metabolic syndrome [3]. WHO criteria differ from ATP III criteria in that they require the presence of insulin resistance as part of the diagnosis. In addition, WHO criteria use different blood pressure cutpoints (greater than 140/90 mm Hg), different high-density lipoprotein (HDL) cholesterol levels (less than 35 mg/dL in men, less than 39 mg/dL in women), and include proteinuria as a risk factor (a urinary albumin excretion rate greater than 20 mcg/min or an albumin/creatinine ratio greater than 30 mg/g). The WHO Clinical Criteria for Metabolic Syndrome include the presence of insulin resistance, which is identified by one of the following [3]:

- Type 2 diabetes
- IFG
- IGT
- For those with normal fasting glucose levels (<110 mg/dL), glucose uptake below the lowest quartile for background population under investigation under hyperinsulinemic, euglycemic conditions

In addition, patients must have at least 2 of the following in order to be diagnosed with metabolic syndrome [3]:

- Antihypertensive medication and/or high blood pressure (≥140 mm Hg systolic or ≥90 mm Hg diastolic)
- Plasma triglycerides ≥150 mg/dL
- HDL cholesterol <35 mg/dL in men or <39 mg/dL in women
- Body mass index (BMI) >30 kg/m2 and/or waist:hip ratio >0.9 in men, >0.85 in women
- Urinary albumin excretion rate ≥20 μg/min or albumin:creatinine ratio ≥30 mg/g

AMERICAN COLLEGE OF ENDOCRINOLOGY PANEL

In 2003, the American College of Endocrinology (ACE) also described a metabolic syndrome, which they refer to as insulin resistance syndrome. The ACE emphasizes that there are no set diagnostic criteria for this syndrome but rather a constellation of abnormalities that raise the risk of adverse outcomes. Their statement describing the insulin resistance syndrome suggests that a patient with two or more of the following is probably insulin resistant and at elevated cardiovascular risk, although the possibility of increased risk should not be excluded in patients who do not fulfill this criterion [4]:

- IFG and/or IGT
  - Fasting: 110–125 mg/dL
  - 120-minute post-glucose challenge: 140–200 mg/dL
- Triglyceride greater than 150 mg/dL
- HDL cholesterol
  - Men: less than 40 mg/dL
  - Women: less than 50 mg/dL
- Blood pressure greater than 130/85 mm Hg

The ACE criteria omit central adiposity (an important component in the ATP III and WHO definitions) and include a 2-hour post-glucose challenge.

THE INTERNATIONAL DIABETES FEDERATION

The International Diabetes Federation offers yet another definition of the metabolic syndrome [126]. Their criteria, published in 2006, are intended to serve as a "worldwide definition" easily used in everyday practice. How widely these criteria will be used remains to be seen. The International Diabetes Federation Consensus Worldwide Definition of the Metabolic Syndrome includes the presence of central obesity, which is defined as a waist circumference ≥94 cm for Europid men and ≥80 cm for Europid women, with ethnicity specific values for other groups [126]. Metabolic syndrome is diagnosed when this sign is positive in addition to any two of the following four factors [126]:

- Elevated triglyceride level (≥150 mg/dL) or specific treatment for this lipid abnormality
- Reduced HDL cholesterol (<40 mg/dL in males or <50 mg/dL in females) or specific treatment for this lipid abnormality
- Elevated blood pressure (systolic blood pressure ≥130 or diastolic blood pressure ≥85 mm Hg) or treatment of previously diagnosed hypertension
- Elevated fasting plasma glucose ≥100 mg/dL or previously diagnosed type 2 diabetes. If fasting plasma glucose is greater than 100 mg/dL, an oral glucose tolerance test is strongly recommended but is not necessary to define presence of the syndrome.

At present, the NCEP ATP III criteria are widely used in research. However, the other definitions are also used in some studies, making it important to note the diagnostic criteria used when reading the medical literature.

EPIDEMIOLOGY

AGE

Approximately 47 million adults in the United States have metabolic syndrome. This represents nearly 1 in 4 adults older than 21 years of age and more than 40% of adults 60 years of age and older [5]. Using the adult definition, approximately 2 million adolescents have metabolic syndrome [6].

GENDER/RACE

Among whites, the age-adjusted prevalence for metabolic syndrome is 24.8% among men and 22.8% among women. Minority populations are disproportionately affected. Prevalence in African American women is 57% higher than in African American men (16%), and Mexican American women have a prevalence that is 26% higher than in Mexican American men. Mexican Americans in general have the highest age-adjusted prevalence (31.9%) [5].

The syndrome has been increasing significantly due largely to the increase in obesity. As the incidence of obesity continues to increase, metabolic syndrome will become more prevalent. Estimates show that about 34% of the adult population is overweight, and 32% are obese [7].

COSTS

The costs of metabolic syndrome are not yet well established. However, healthcare expenses related to metabolic syndrome symptoms and/or risk factors are significant. Among participants 65 years of age and older in the large Cardiovascular Health Study, Medicare costs were 20% higher for those with metabolic syndrome compared to those without the syndrome. The increase was primarily due to costs attributed to the individual risk factors of abdominal obesity, low HDL, and elevated blood pressure [68]. Obesity costs alone are estimated to be at least $117 billion annually [69]. The medical expenditures and lost productivity attributable to diabetes are estimated at $174 billion, with $116 billion in direct medical expenditures [8]. The health costs associated with hypertension and dyslipidemia are also significant.

PATHOPHYSIOLOGY/ETIOLOGY

The precise cause of metabolic syndrome is unknown, and in fact, there may be more than one underlying cause. Various hypotheses exist, including possible elevated levels of cortisol, insulin resistance, and subsequent compensatory hyperinsulinemia [9]. Some evidence shows increased cortisol to cause insulin resistance. Another theory is related to the belief that visceral or central adiposity causes an increase in free-fatty acid flux in the portal and systemic circulations. Such fat distribution may also result in inflammatory, prothrombic, and fibrinolytic activity. The enhanced lipolytic activity of visceral adipocytes increases free-fatty acid flux to the liver and stimulates very low-density lipoprotein (LDL) production. It may also exacerbate hepatic glucose production through increased gluconeogenesis and decreased insulin sensitivity. High free-fatty acid levels inhibit glucose uptake by muscles and inhibit hepatic insulin clearance.

The insulin resistance, which is often associated with metabolic syndrome, may then decrease lipoprotein lipase and result in impaired clearance of LDL particles. In addition, the oxidative stress within the arterial intima and endothelium may result in atherosclerotic changes [128; 129].

Certainly, improper nutrition and inadequate physical activity cause several of the criteria that eventually result in metabolic syndrome. The precise triggering agents are still being examined.

RISK FACTORS

As noted earlier, risk factors involved in metabolic syndrome include dyslipidemia, obesity, and insulin resistance. Each is addressed briefly below and will be discussed in more detail later in the text.

DYSLIPIDEMIA

Dyslipidemia is an important aspect of the syndrome. The criteria for metabolic syndrome include elevated triglycerides and low HDL; hypercholesterolemia may also be present but is not included in the definition.

Often, the metabolic syndrome patient has normal levels of LDL, although the LDL particles are typically smaller in size and denser in nature. These characteristics are believed to make them more atherogenic.

OBESITY/CENTRAL ADIPOSITY

Obese patients are much more likely to have metabolic syndrome. Metabolic syndrome affects 50% to 60% of obese men and women, compared with 4.5% to 6% of men and women who are normal weight [5].

One apparent foundation of metabolic syndrome is excess deposition of adipose tissue, which may give rise to an insulin resistant state. Adipose tissue secretes leptin, tumor necrosis factor, and free-fatty acids that diminish the effects of insulin. In addition, leptin appears to impair insulin release by pancreatic beta cells. Leptin is believed to promote angiogenesis, oxidative stress in endothelial cells, and vascular cell calcification. Cytokines secreted from adipose tissue may initiate a proinflammatory state that promotes endothelial dysfunction.

Of note, accumulation of intra-abdominal fat, irrespective of whether a person is overweight or not, may result in insulin resistance and contribute to metabolic syndrome [10]. Individuals in the upper-normal weight and slightly overweight BMI range have a relatively high prevalence of insulin resistance and are at increased risk of having metabolic syndrome, thus increasing the risk of diabetes and CV disease.

Although BMI is important in the discussion of metabolic syndrome, there is a growing body of evidence demonstrating the impact of central adiposity on diabetes risk. Wang and colleagues compared BMI, waist circumference, and waist-to-hip ratio in predicting development of type 2 diabetes [61]. Researchers used information collected in the Health Professionals Follow-Up Study, a prospective cohort study of 27,270 men who were followed for 13 years. During the follow-up period, 884 men developed type 2 diabetes. Waist circumference was the best predictor. Men with waists greater than 34 inches were twice as likely to develop diabetes compared to men with smaller waist sizes (<34 inches); men with waist sizes greater than or equal to 40 inches were more than 12 times more likely to develop diabetes than men with smaller waist sizes [61]. In another study, Bray and colleagues looked at waist circumference, waist-to-hip ratio, and central and subcutaneous adipose tissue measured by computed tomography (CT) as predictors of diabetes in people participating in the Diabetes Prevention Program [70]. They found that waist-to-hip ratio and waist circumference predicted diabetes; CT measurement of central adiposity also predicted diabetes but was not found to offer an important advantage over the simpler measurements. Subcutaneous adiopose tissue, on the other hand, did not predict diabetes.

This information is of particular importance because individuals may or may not be considered overweight based solely on BMI. Therefore, the additional information of waist circumference helps to determine health risks.

INSULIN RESISTANCE

In some cases, metabolic syndrome and insulin resistance syndrome are incorrectly equated to be the same condition, which they are not. Based on available data, there is not sufficient evidence to show that insulin resistance causes all of the metabolic risk factors associated with metabolic syndrome.

Insulin is a regulator of the metabolism of carbohydrates, lipids, and proteins. Any impairment in insulin action may have metabolic consequences. Insulin resistance may affect arterial muscle, reducing responsiveness to vasoactive stimuli. Hyperinsulinemia as a response to insulin resistance may also promote sodium resorption by the kidneys [71].

Studies have shown that insulin-secretory ability predicts the risk of developing type 2 diabetes—with a 3-fold increase in risk in persons with low insulin secretion and a 5-fold increase in persons with insulin resistance [11]. In a 2006 study, participants in the San Antonio Heart Study were evaluated for insulin resistance and insulin secretion [72]. The researchers tested fasting plasma glucose and then performed oral glucose tolerance tests in 1282 patients who were non-diabetic (normal fasting glucose and normal glucose tolerance) at baseline. Patients with a combination of higher resistance and lower secretion at baseline were most likely to develop diabetes during the 7 to 8 years of follow-up.

The number of patients with metabolic syndrome is greater than the number of patients with type 2 diabetes or those with IGT. The presence of metabolic syndrome does, however, put patients at an increased risk for developing diabetes. A follow-up analysis of the San Antonio Heart Study found that patients who went on to develop diabetes had significantly greater baseline BMI, waist circumference, triglyceride level, and blood pressure and significantly lower baseline HDL than patients who did not go on to develop diabetes. This study also found that both the WHO and NCEP ATP III definitions predicted diabetes independently of age, sex, ethnic origin, or family history [73]. The risk was particularly high in patients with both IFG and metabolic syndrome but was also elevated in people with metabolic syndrome but not IFG.

METABOLIC SYNDROME AND CARDIAC RISK

Cardiovascular disease remains the most common cause of death in both men and women in the United States—precipitating more than one-half of all deaths [56]. Metabolic syndrome significantly increases the risk of CV disease. In the past, it was thought that the overall risk of coronary heart disease in those with metabolic syndrome may be greater than the risk attributable to the individual components. Some studies support this theory, but others suggest this is likely not the case. However, metabolic syndrome may add additional risk in the presence of other traditional CV risk factors, making it a potentially useful composite of its component parts [12; 72; 74]. Post-hoc analysis of both the Scandinavian Simvastatin Survival Study (4S) and the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) showed that patients with metabolic syndrome (but not type 2 diabetes) had at least a 1.4 times greater risk of coronary events than those without metabolic syndrome [13]. Risk increased when type 2 diabetes developed. The presence of metabolic syndrome increased the risk of major coronary events irrespective of 10-year absolute coronary risk above or below 20%.

A review of National Health and Nutrition Examination Survey (NHANES) data revealed that in patients younger than 50 years of age, the age-adjusted prevalence of CV disease was highest in patients with both type 2 diabetes and metabolic syndrome (19.2%), followed by patients with metabolic syndrome but not type 2 diabetes (13.9%) [14]. The prevalence of CV disease was no higher in patients with type 2 diabetes without metabolic syndrome than in individuals who had neither type 2 diabetes nor metabolic syndrome.

In the Kuopio Ischemic Heart Disease Risk Factor study, data from more than 1200 men without CV disease at baseline showed that the presence of metabolic syndrome was associated with a relative risk of 3.77 for mortality from coronary heart disease [15]. It also showed a relative risk of 2.43 for all-cause mortality compared with the absence of the syndrome. In an analysis of the West of Scotland Coronary Prevention Study, hazard ratios for coronary events increased with an increasing number of metabolic syndrome factors, from 1.79 for one factor, 2.25 for two factors, 3.19 for three factors, and 3.65 for four or more factors [62].

The Cardiovascular Health Study, a prospective cohort study of older adults in the United States, found that people with metabolic syndrome had a 20% to 30% increased risk of any CV disease event (coronary heart disease [CHD], congestive heart failure, or stroke) over a median of 11 years of follow-up [79]. Regarding CV disease mortality (from CHD, cerebrovascular disease, heart failure, or peripheral vascular disease), however, this study found that the combination of hypertension and elevated fasting glucose predicted CV mortality better than metabolic syndrome [80].

It should be noted that not all studies have compared the risk from metabolic syndrome to that conveyed by the Framingham Risk Score or other methods of calculating CV risk. The Atherosclerosis Risk in Communities study, which followed participants for an average of 11 years, showed that the risk of CHD was increased about 1.5 to 2 times in people with metabolic syndrome, after adjustment for risk factors including age, smoking, LDL cholesterol, and race. In this study, however, metabolic syndrome did not add to the risk indicated by the Framingham Risk Score [78]. A 2005 report by Wannamethee and colleagues, using data from a 20-year prospective study of 5128 men, found that the Framingham Risk Score was a more sensitive predictor of coronary heart disease at both 10- and 20-year follow-up [81]. Adding metabolic syndrome to a model including the Framingham Risk Score did not provide additional predictive value. On the other hand, metabolic syndrome was a more sensitive predictor of diabetes mellitus.

Although it may or may not improve upon other risk measurements, metabolic syndrome may be a useful gauge encouraging early intervention. Three meta-analyses, incorporating studies published through 2005, have confirmed that metabolic syndrome increases the risk of CV disease, with relative risks from 1.53 to 2.18 [75; 76; 77].

Along with cardiac disease and diabetes, patients with metabolic syndrome also may be at risk for other conditions such as fatty liver, cholelithiasis, polycystic ovarian syndrome, gout, chronic kidney disease, and asthma [3; 82; 83; 84; 85; 86; 87].

DIAGNOSIS/SCREENING

EVALUATION

A patient history and physical examination are critical in the diagnosis, evaluation, and management of any disease. For metabolic syndrome, there are usually no immediate physical symptoms or specific complaints. The medical problems tend to develop rather innocuously over time. The history must include a thorough discussion of past medical conditions as well as current risk factors.

Evaluation of patients for metabolic syndrome should include measurement of:

- Vital signs
- Height
- Body weight
- BMI
- Waist circumference

With respect to laboratory tests, along with basic serum chemistry and complete blood count, there should be a measurement of fasting blood sugar as well as a lipid profile. The lipid profile includes total cholesterol, HDL cholesterol, LDL cholesterol, and triglyceride. In some cases, the lipid panel report will include additional calculated values such as HDL/total cholesterol ratio or a risk score based on lipid profile results, age, gender, and other risk factors.

The ATP III panel did not find evidence to recommend routine measurements of insulin resistance, proinflammatory state, or prothrombotic state [2]. In 2004, the AHA teamed with the ADA and the NHLBI and recommended that the Framingham algorithm be used to estimate cardiovascular risk in patients with metabolic syndrome [16]. The risk for thrombotic events can be reduced by aspirin therapy, and the AHA currently recommends aspirin prophylaxis in most patients whose 10-year risk for coronary heart disease is 10% or greater according to the Framingham risk scoring.

EVIDENCE-BASED PRACTICE RECOMMENDATION

The USPSTF strongly recommends that clinicians routinely screen men 35 years of age and older and women 45 years of age and older who are at increased risk of coronary heart disease for lipid disorders.

(http://www.ahrq.gov/clinic/uspstf/uspschol.htm. Last accessed October 16, 2008.)

Strength of Recommendation: A (The USPSTF strongly recommends that clinicians provide this service to eligible patients based on good evidence.)

On exam, Mr. G is 5'11" and 210 lbs. His BMI is 29. This classifies him as overweight.

(BMI is used to define overweight and obesity, which is weight-adjusted for height. It is calculated by [weight in kg] divided by [height in meters]^2 OR weight [pounds]/height [inches]^2 x 703. A BMI of 25.0 or greater is defined as overweight, and a BMI of 30.0 or more is considered obese.)

His waist circumference is 40.5 inches, and his blood pressure is 135/80 mm HG (sitting) and 130/80 mm Hg (standing). His heart rate is 86 beats per minute, his temperature is 98.6° Fahrenheit, and his respiration is 18 breaths per minute. His physical exam is unremarkable.

Laboratory data as follows:

- *Total cholesterol: 230 mg/dL*
- *HDL: 38 mg/dL*
- *LDL: 152 mg/dL*
- *Triglycerides: 200 mg/dL*
- *Glucose (fasting): 120 mg/dL*

Based on his waist circumference, IFG, decreased HDL, and increased triglyceride, Mr. G. meets the definition of metabolic syndrome. Aggressive treatment of the risk factors is warranted.

GENERAL TREATMENT

As discussed, metabolic syndrome predisposes patients to type 2 diabetes and coronary artery disease. Complications can occur as early as a decade after development of the syndrome. Treating the elements of metabolic syndrome is useful because it can prevent and/or reduce the risk the development of coronary artery disease and type 2 diabetes.

Treatment consists of the correction of the individual components, with weight loss as a major goal. Weight loss improves all aspects of metabolic syndrome. Weight loss of 5% to 10% can lead to significant reductions in morbidity and mortality. The goal of treatment is to prevent or ameliorate diabetes, hypertension, and CV disease. Therefore, the first step in treatment is effective lifestyle interventions, focusing on nutrition and exercise.

EVIDENCE-BASED PRACTICE RECOMMENDATION

The European Society of Cardiology recommends that the main emphasis in the management of metabolic syndrome should be in professionally supervised lifestyle changes, particularly efforts to reduce body weight and increase physical activity.

(http://www.guideline.gov/summary/summary.aspx?ss=15&doc_id=4766. Last accessed October 16, 2008.)

Level of Evidence: Consensus Statement/Expert Opinion.

NUTRITION

Nutritional advice is critical in the management of metabolic syndrome. Most clinicians, however, are not well informed about the principles of healthy eating. Healthcare professionals must learn the latest research and recommendations concerning carbohydrates, fats, and protein. With this information, one can provide useful advice to patients about healthy eating.

Despite skepticism by some clinicians, providing dietary information to patients has been found to be an effective intervention. The U.S. Preventive Services Task Force (USPSTF), an independent panel of experts in primary care and prevention that systematically reviews the evidence of effectiveness and develops recommendations for clinical preventive services, found good evidence that medium- to high-intensity counseling interventions can produce medium-to-large changes in average daily intake of core components of a healthy diet (including saturated fat, fiber, fruit, and vegetables) among adult patients at increased risk for diet-related chronic disease [17]. Intensive counseling interventions have been examined in controlled trials among at-risk adult patients. These trials combined nutrition education with behavioral dietary counseling provided by a nutritionist, dietitian, or specially trained primary care clinician (e.g., physician, nurse, or nurse practitioner). The USPSTF concluded that such counseling is likely to improve important health outcomes and that benefits outweigh potential harms [17]. Assessing dietary patterns and recommending change is critical for success.

EVIDENCE-BASED PRACTICE RECOMMENDATION

The USPSTF recommends intensive behavioral dietary counseling for adult patients with hyperlipidemia and other known risk factors for cardiovascular and diet-related chronic disease. Intensive counseling can be delivered by primary care clinicians or by referral to other specialists, such as nutritionists or dietitians.

(http://www.ahrq.gov/clinic/uspstf/uspsdiet.htm. Last accessed October 16, 2008.)

Strength of Recommendation: B (The USPSTF recommends that clinicians provide this service to eligible patients based on fair evidence.)

Reduction in Calories

One of the most important components relating to nutritional advice for overweight patients is reduction of calories. Patients should understand that the energy stored in food is measured in terms of calories. One calorie is the amount of energy required to raise the temperature of 1 gram of water 1°C. Most people's daily caloric requirement is less than 2000 calories. As a quick rule of thumb, patients can calculate the number of daily calories they require by multiplying their current weight by 13 (or 15 if one is active). Overweight patients must reduce the number of consumed calories in order to lose weight. Reduction in calories is the most important dietary component of weight loss.

Between 1971 and 2000 in the United States, average daily caloric intake rose for men and women, and a high portion of the extra calories was from carbohydrates, according to data from NHANES [18]. Between 1999 and 2000, women consumed 1877 calories a day on average, or 22% more calories than their average daily consumption between 1971 and 1974. Men's caloric intake increased by 7% to 2618 calories per day over the same period. In 2000, women consumed 355 more calories each day than women in 1971, and men ate 168 more calories each day in 2000 than men in 1971. A more recent look at NHANES data, going up to 2002, found that Americans have been consuming both increasingly larger amounts of food and more energy-dense foods than in earlier years [89]. On average, U.S. residents were 25 lbs heavier in 2002 than they were in 1960. The average weight for men increased to 191 pounds in 2002 from 166.3 pounds in 1960. In women, the average weight increased to 164.3 lbs from 140.2 lbs during the same period [90]. This is largely due to an increase in daily calorie consumption.

When recommending reduction in calories, specific guidelines should be kept in mind. Patients with a BMI between 27 and 35 should reduce their total calorie intake by 300–500 daily. Patients with a BMI greater than 35 should reduce their total calories by 500–1000 daily. This reduction will produce the recommend weight loss of 1–2 lbs per week in most patients.

Portion control is also a key to weight loss. Hannum and colleagues demonstrated that portion control showed the greatest weight loss in women over a 24-month period, more than reduced dietary fat consumption, increased fruit and vegetable consumption, or increased physical activity [19]. Thirty-eight percent of obese patients who consistently practiced food portion control lost 5% or more of their baseline weight, while 33% of patients who did not consistently practice portion control gained 5% or more of their baseline weight. A 2006 study by the same researchers involving overweight and obese men showed that using controlled portions of food led to more weight loss than a self-selected diet based on the food guide pyramid [91].

Dietary Reference Values

Since the 1990s, the Institute of Medicine (IOM) has issued a series of reports that suggest dietary reference values for intake of nutrients. One of these reports, updated in 2005, establishes the Dietary Reference Intakes (DRI) for energy, carbohydrates, fiber, fat, fatty acids, cholesterol, protein, and amino acids. The following ranges are recommended in the 2005 report for percentage of daily caloric intake [21]:

- Carbohydrates: 45% to 65%
- Sugars: No more than 25%
- Fats: 20% to 35%
- Protein: 10% to 35%
- Fiber: Men younger than 50 years of age should receive 38 g of fiber; women younger than 50 years of age need 25 g. Men older than 50 years of age should receive 30 g of fiber; women older than 50 years require 21 g.

Patients should be aware of these values and keep them in mind when designing a nutritional program. Reviewing and modifying nutritional intake is one of the most important steps in helping patients lose weight. It is not about dieting but rather a lifestyle of healthy eating. The issue is not low carbohydrate versus low fat. Rather, it is a spectrum of choices.

With all the publicity regarding various diets, patients should be advised that it is as important to include certain foods as it is to exclude others. "Fad diets" typically exclude certain foods and therefore often have nutrition deficiencies. For example, high-fat, low-carbohydrate diets are low in vitamin E, vitamin A, thiamin, folate, calcium, magnesium, and zinc. Low-fat diets are typically deficient in vitamin B12.

Studies have been published comparing popular diets. Researchers at Tufts-New England Medical center randomized patients to the Atkins, Ornish, Weight Watchers, and Zone diets to evaluate their effects on weight loss and reduction in cardiac risk [64]. The study involved 160 patients ranging in age from 22 to 72 years. All had at least one risk factor for heart disease, such as hypertension, dyslipidemia, or fasting hyperglycemia, and all were either overweight or obese. Patients received counseling on their plans for 2 months and then followed the diet on their own for 10 months.

At the end of 1 year, all the patients decreased their weight by approximately 4%. In addition, all groups showed both a reduction in LDL cholesterol and an increase in HDL levels. Moreover, all patients who completed the study showed some reduction in risk of heart disease at 1 year, irrespective of diet. However, by 1 year, approximately one-half of the patients enrolled in the Atkins and Ornish programs had dropped out, and one-third of patients in the Weight Watchers and Zone program had quit.

Another study compared the Atkins, Ornish, Zone, and LEARN diets in overweight and obese women [98]. Women on the Atkins diet lost the most weight (4.7 kg at 12 months), but the difference between diets was significant only for Atkins versus Zone. Also at 12 months, changes in LDL cholesterol were not significantly different among the groups.

Stern and colleagues randomized 132 patients with a BMI greater than 35 to either a low-carbohydrate diet (less than 30 g/d) or a low-fat diet (less than 30% calories from fat) [99]. Although the low-carbohydrate group lost more fat at 6 months, both groups had the same weight loss at 1 year (3–4 kg). Of note, there was no difference between groups in total and LDL cholesterol levels. Both groups had a dropout rate of nearly one-third.

Instead of counseling patients about specific diets, it is more useful to focus on healthy eating.

Dietary Guidelines

In January 2005, the U.S. Department of Health and Human Services in conjunction with the U.S. Department of Agriculture issued the sixth edition of the Dietary Guidelines for Americans [20]. The guidelines are revised every 5 years. A rigorous process, utilizing the best scientific evidence, was used to develop these guidelines. A 13-member independent committee of experts prepared a report for review by government scientists and officials, who subsequently made the report available to the public and invited comment. Additional expert review occurred and the Dietary Guidelines were established. The focus is to help the public make healthy food choices, maximizing nutrition and balancing eating and physical activity.

More than 40 specific recommendations were made, based on nine general topics [20]:

- Adequate nutrition within caloric needs
- Weight management
- Physical activity
- Food groups that should be encouraged
- Fats
- Carbohydrates
- Sodium and potassium
- Alcoholic beverages
- Food safety

Overall, a healthy eating plan is one that emphasizes fruits, vegetables, and whole grains and includes lean meats, poultry, fish, beans, eggs, and nuts [20]. In addition, the plan should be low in saturated fats, trans fats, cholesterol, sodium, and added sugars.

The key recommendations include [20]:

(Recommendations are based on a 2000-calorie daily intake. Patients can calculate their specific caloric requirements at http://www.healthierus.gov/dietaryguidelines.)

- Two cups of fruit and 2½ cups of vegetables per day are recommended. This should include variety, focusing on all five vegetable subgroups (dark green, orange, legumes, starchy vegetables, and other vegetables).
- Three or more ounces of whole-grain products are recommended each day.
- Three cups per day of fat-free or low-fat milk or equivalent milk products should be included.
- Fewer than 10% of calories should come from saturated fatty acids; trans fatty acids should be avoided.
- Total fat intake should not exceed 20% to 35% of calories. Preferred fat sources are fish, nuts, and vegetable oils containing polyunsaturated and monounsaturated fatty acids. Lean, low-fat, or fat-free meats, poultry, dry beans, and milk are preferred.
- Minimize added sugar or caloric sweetener.
- Consume less than 2300 mg (approximately one teaspoon of salt) of sodium daily. Limit salt added in food preparation.
- Choose potassium-rich fruits and vegetables.
- Alcohol should not exceed one drink per day for women or two drinks per day for men.
- Wash hands, food contact surfaces, and fruits and vegetables to avoid microbial foodborne illness, but do not wash or rinse meat and poultry.
- Avoid raw (unpasteurized) milk, egg, or meat products, unpasteurized juices, and raw sprouts.

A quick way for patients to remember these recommendations can be:

- Focus on fruits.
- Vary your veggies.
- Get your calcium-rich foods.
- Make half your grains whole.
- Go lean with protein.

With respect to children, those 2 to 8 years of age should consume 2 cups daily of fat-free or low-fat milk, and those 9 years of age or older should consume 3 cups of milk daily [20]. Fat intake should be limited to less than 300 mg of cholesterol. No more than 20% to 35% of calories should be from fat, and less than 10% should be from saturated fat.

In conjunction with the revised Dietary Guidelines, the U.S. Department of Agriculture issued a revised food pyramid. The new MyPyramid replaces the original Food Guide Pyramid [57]. The MyPyramid Food Guidance System provides food-based guidance to help implement the recommendations of the Dietary Guidelines. It translates the Guidelines into a total diet that meets nutrient needs from food sources and aims to moderate or limit dietary components often consumed in excess. The new pyramid focuses on the fact that one size does not fit all and instead provides a personalized approach. MyPyramid includes the following parts: Activity, Moderation, Personalization, Proportionality, Variety, and Gradual Improvement. Patients should be encouraged to view the website (http://www.mypyramid.gov) to develop a personalized plan.

Currently, Mr. G snacks with sugary treats throughout the day, as he does not take time to eat breakfast and frequently goes without lunch. By the time he eats dinner relatively late in the evening, he is famished and tends to overeat. Mr. G has very little nutritional information. Either the physician can provide some basic dietary information, or the patient can be referred to a dietitian. Mr. G first should understand roughly how many calories he is consuming per day. His goal should be to consume no more than 2000 calories a day. He may wish to keep a food log for 2 to 3 days to get a better idea of exactly how much he is eating.

This log could be reviewed at the next visit. He should divide the recommended calories over at least 3 meals. Eating breakfast should be emphasized, as there is data that supports the premise that eating breakfast helps to maintain one's weight rather than cause weight gain. In addition, he should minimize snacking. Because he consumes a fair amount of soda, simply eliminating one can of soda a day could lead to a 5–10 lb weight loss over the course of a year. The emphasis should be on gradual lifestyle changes.

PHYSICAL ACTIVITY

Frequency/Intensity

Physical activity is essential in treating metabolic syndrome. It has been shown to reduce obesity, improve blood pressure control, improve lipid profile, and reduce insulin resistance. When discussing exercise, it is important to focus on frequency (how often and how long) as well as intensity. The U.S. Surgeon General recommends 30 minutes of physical activity on most days of the week [65]. The AHA recommends 30 minutes of moderate physical activity 5 days a week or 20 minutes of vigorous activity three days a week and also suggests that resistance training or other strengthening activities be performed on two or more nonconsecutive days each week. [66].

According to the IOM, adults should set a long-term goal of at least 60 minutes of moderate-intensity physical activity on at least 5 days of the week [21]. This is an increase from 30 minutes recommended by the U.S. Surgeon General. In addition, the recommendations from the federal government described in the U.S. Dietary Guidelines suggest a minimum of 30 minutes but recommend 60 minutes to maintain fitness and prevent weight gain.

Patients often want to know how intense their activity should be. Physiologically, intensity refers to relative load or resistance against which a muscle works. One important point is for patients to elevate their heart rate. In their recommendations, the AHA provides a simple way to gauge intensity. Moderate activity, such as a brisk walk, will noticeably elevate the heart rate. Vigorous activity, for example jogging, causes rapid breathing and substantially raises the heart rate. Moderate exercise can be accumulated in increments of 10 minutes or more. Moderate and vigorous activity can be combined to meet the weekly recommendations; the AHA offers a chart with examples of different types of exercise and details about how to judge the total amount per week [66].

The following advice regarding exercise can be given to patients:

- *Plan to exercise a minimum of 3 days per week.* Patients can slowly add days as they become more comfortable. The goal should be to exercise 5 days a week or more.
- *Start off with 10 to 15 minutes of exercise on the days you exercise, and increase the time to 60 minutes daily over a few months.* Everyone can find 10 to 15 minutes a few days a week. Encourage patients to make it a part of their schedule. The key is to help them find activities that they enjoy. Exercise should not be viewed as a burden or a chore.
- *Alternate between flexibility, aerobic, and resistance training.* By doing this, patients will target all the major muscle groups.

Clinicians should consider writing these recommendations on a prescription pad or a special form. Patients are more likely to follow this advice when it is written down. In addition, consider asking patients to keep a journal or log when they begin an exercise program, which can be reviewed on the next visit. There must be regular discussion about physical activity at each office visit. Continuous long-term care is essential.

Fitness

It is important to stress to patients that physical activity, even without weight loss, can reduce the risks of developing heart disease and type 2 diabetes. Some studies indicate that one may be overweight and "fit" if they exercise regularly. Wessel et al. studied 906 women who were being evaluated for coronary artery disease [22]. He found that women with low fitness levels were

46% more likely to have a coronary event than those with high fitness levels. Overweight women who were fit had better outcomes than unfit thin women. More and more data point to the notion that low cardiorespiratory fitness is an established risk factor for cardiovascular and total mortality. Carnthenon studied 4400 patients who were given a treadmill test between the ages of 18–30 years as part of the Coronary Artery Risk Development in Young Adults (CARDIA) study. They were then followed for an average of 15 years [23]. Researchers found that 60% of the women and 50% of the men who had low fitness levels in their twenties had double the risk of developing diabetes, metabolic syndrome, and high blood pressure by the end of the study.

Blair et al. used the observational cohort study design to calculate all-cause death rates in men with diabetes across quartiles of fitness and BMI categories. Study participants were 2196 men with diabetes (average age: 49.3 years) who underwent a medical examination, including a maximal exercise test, during 1970 to 1995, with mortality follow-up to the end of 1996 [24]. At the conclusion of the study, obese but moderately fit men had one-third the death rate of normal weight but unfit men. The researchers later stratified participants by BMI category and found that, within each category, cardiorespiratory fitness greatly attenuated the effect of metabolic syndrome on both all-cause and cardiovascular disease mortality [103].

Katzmaryzk studied 15,466 healthy men and 3757 men with metabolic syndrome over a 10-year period to determine the relationship between cardiorespiratory fitness and mortality [25]. Compared with the healthy subjects, men with metabolic syndrome had twice the risk of dying from CV disease and 1.3 times the risk of dying from other causes. However, if they were fit, their risks were similar to healthy men. A significant dose-response relationship between cardiorespiratory fitness and mortality was observed in men with metabolic syndrome. It appears that cardiorespiratory fitness could attenuate the mortality risk associated with metabolic syndrome.

In a similar study of more than 7000 women, Farrell et al. studied the prevalence of metabolic syndrome across age strata and cardiorespiratory fitness levels in women [26]. Researchers found that the prevalence of metabolic syndrome was markedly lower across progressively higher levels of fitness in women of different age groups. Because regular physical activity improves components of metabolic syndrome, modest increases in cardiorespiratory fitness among low-fit women may ameliorate metabolic syndrome in some instances—similar to the results observed in men.

Studies continue to support the connection between low levels of fitness and metabolic syndrome, and some have shown that the connection is independent of BMI. Hassinen and colleagues, studying a population sample of 671 men and 676 women 57 to 79 years of age, found a strong inverse relationship between maximal oxygen uptake (VO2max) during a bicycle exercise test and the presence of metabolic syndrome [100]. Adjusting for BMI weakened the association but did not eliminate it, although adjusting for waist circumference made the association non-significant in men. Brouwer and colleagues examined baseline data from the Second Manifestations of ARTerial disease (SMART) study, an ongoing cohort study of patients with cardiovascular disease or risk factors [101]. Looking at patients who already had evidence of cardiovascular disease, they showed that patients who were more physically active were less likely to have metabolic syndrome and insulin resistance. The association remained after adjusting for age, sex, BMI, and smoking.

In a cohort study following 9007 men and 1491 women who were initially free of metabolic syndrome, LaMonte and colleagues demonstrated that low cardiovascular fitness may predict development of the syndrome [102]. They stratified participants according to BMI and found that overweight and obese men in the top two-thirds of the fitness distribution had approximately a 42% lower risk of developing metabolic syndrome than similar men in the lower one-third. For normal weight men, the decrease was about 21%. There was a similar but non-significant trend for women [102].

Weight loss can be an important part of the management of metabolic syndrome. In a retrospective review of 125 obese patients (who also met the criteria for metabolic syndrome) enrolled in a weight-loss program, a mean weight loss of 15% of initial body weight improved all components of metabolic syndrome: systolic blood pressure was reduced by 14.6 mm Hg, fasting glucose decreased by 19 mg/dL, and triglyceride improved dramatically [27]. As noted, weight reduction of as little as 5% body weight (often as little as 5 to 10 lbs) is associated with lower incidence of diabetes, reduced blood pressure, and improved dyslipidemia. In a randomized, controlled trial comparing treatment with the weight-loss drug sibutramine, lifestyle modifications, or combination of the two, each 1 kg of weight loss was associated with an 8% reduction in the odds of metabolic syndrome at one year, after controlling for demographic variables, baseline metabolic syndrome status, and treatment group [104]. Study participants were 180 women and 44 men, 18 to 65 years of age, with BMI 30–45 and no uncontrolled hypertension or type 1 or 2 diabetes.

Currently, Mr. G is not physically active. He does not engage in any type of exercise. After a discussion of activities he either enjoys or might enjoy, it is agreed that he should begin a walking routine. He will begin walking with a goal of 30 minutes per day, with an initial goal of 3 days a week. Because he has been mostly sedentary, he can try to break the 30 minutes down into three 10-minute segments or two 15-minute segments, gradually building up to 30 minutes, and eventually 60 minutes, 5 days of the week. A program of interest to some patients is the 10,000 steps a day program. This is based on studies showing that a daily regimen of 10,000 steps can improve cardiovascular fitness and improve glycemic control. Depending upon stride, walking 10,000 steps is roughly equivalent to 5 miles. As a reference, most people average less than 5000 steps a day, so 10,000 steps will represent a significant increase in activity. Mr. G's physician suggests that he start wearing a pedometer without changing activity level so a baseline can be obtained. For about 3 to 4 days, Mr. G writes down the amount at the end of each day, and calculates the average daily step count. As a weekly goal, he adds an additional 500 steps per day. His physician advises him to increase the number of steps until he reaches 10,000 steps per day. After a few weeks, Mr. G can add some resistance type exercises, such as pushups or workouts with light dumbbells.

CONSIDERATIONS FOR NON-ENGLISH PROFICIENT PATIENTS

As a result of the evolving racial and immigration demographics in the United States, interaction with patients for whom English is not a native language is inevitable. Because patient education is such a vital aspect of the management and prevention of metabolic syndrome, it is each practitioner's responsibility to ensure that information and instructions are explained in such a way that allows for patient understanding. When there is an obvious disconnect in the communication process between the practitioner and patient due to the patient's lack of proficiency in the English language, an interpreter is required.

In this multicultural landscape, interpreters are a valuable resource to help bridge the communication and cultural gap between clients/patients and practitioners. Interpreters are more than passive agents who translate and transmit information back and forth from party to party. When they are enlisted and treated as part of the interdisciplinary clinical team, they serve as cultural brokers, who ultimately enhance the clinical encounter.

TREATMENT OF SPECIFIC CONDITIONS

OBESITY

Treatment for obesity is primarily lifestyle intervention, as described. In 1998, the NHLBI created an evidence-based algorithm to help guide clinicians in identifying and treating obesity [28]. Some of the information in the NHLBI resource is now out-of-date, but it provides a useful starting place when caring for patients who need to lose weight. Other guidelines are available. The ADA offers strategies for weight management through lifestyle modification for both prevention and treatment of type 2 diabetes [105]. The Institute for Clinical Systems Improvement, a non-profit collaborative of healthcare providers and organizations, last updated their guideline on obesity management and prevention in 2006 [106]. The Veterans Administration/Department of Defense clinical practice guideline for screening and management of overweight and obesity may be useful in general practice as well [107]. The American College of Physicians (ACP) has published a guideline on the pharmacologic and surgical management of obesity [108].

Medications

According to NHLBI guidelines, obese patients with a BMI greater than 30 or overweight patients with BMI greater than 27 and concomitant obesity-related risk factors or diseases, such as hypertension, diabetes, or dyslipidemia, are candidates for drug therapy. The ACP's guideline applies to patients with BMI of 30 or greater [108].

Although a useful tool, it is important to remember that medication is only one part of the treatment. There must also be an overall weight management program, including a reduced-calorie diet and increased physical activity. In addition, patients must have realistic expectations of medication therapy and not have contraindications to the drugs.

There are two medications—orlistat and sibutramine—approved by the U.S. Food and Drug Administration (FDA) for long-term treatment of obesity. They can produce modest weight loss (typically 2.6–4.8 kg) that can be sustained for 2 years if the medication is continued [63]. Studies comparing the two medications are limited. A number of small studies have found that both can provide weight loss, with inconsistent results regarding whether one is more effective than the other [109; 110; 111]. The medication should be selected based on individual patient assessment (BMI, other clinical and laboratory values, etc.).

Orlistat is a gastric and pancreatic lipase inhibitor. It reduces the absorption of 30% of a patient's dietary fat intake. It acts by reversibly inhibiting pancreatic, gastric, and carboxyl ester lipases and phospholipase A_2—all of which are required for the hydrolysis of dietary fat in the gastrointestinal tract. A meta-analysis of orlistat versus placebo trials demonstrated that patients treated with orlistat lost 2.5 kg at 6 months and 2.75 kg at 12 months [29]. This data is statistically significant. Like most medications, orlistat does have side effects. The adverse effects of orlistat include fecal urgency, oily spotting, and flatulence [59]. The drug may not be suitable for patients with bowel conditions, such as ulcerative colitis and Crohn's disease, or irritable bowel syndrome. Typical dosage is 120 mg with each meal [59].

Sibutramine is a norepinephrine, dopamine, and serotonin reuptake inhibitor that functions as an appetite suppressant. It is a Schedule IV medication that does not have any addictive properties. A meta-analysis of sibutramine versus placebo trials demonstrated 3.4 kg weight loss at 6 months and 4.45 kg weight loss at 12 months [29]. The data was statistically significant. The adverse effects of sibutramine include an increase in blood pressure and heart rate, as well as headache, dry mouth, and insomnia. The dose-related increase in blood pressure and heart rate must be monitored closely. Typical dosage is 10–15 mg/day [58].

Given that discontinuation of drug therapy often leads to rapid weight regain, the pharmacologic treatment of obesity should only be used as part of a program that includes lifestyle modification interventions, such as intensive diet and/or exercise counseling and behavioral interventions.

The Agency for Healthcare Research and Quality (AHRQ) has conducted an evidence report on pharmacologic treatment of obesity [29]. Weight loss was typically less than 5 kg (11 lbs) at one year. There was no evidence indicating that any one medication promoted more weight loss than any other drug. The choice of drug may be made on an individual basis, based on tolerance to the expected side effects.

Surgery

For some patients who do not achieve weight loss with diet, physical activity, and drug therapy, typically patients with a BMI greater than 40 or greater than 35 with comorbid conditions, surgical intervention may be a consideration [28]. In 2005, based on self-reported data from the Behavioral Risk Factor Surveillance System, about 3.1% of U.S. adults had BMI greater than 40 [113]. This is likely an underestimate, as measured weight tends to be higher than self-reported numbers. In 2004, health examinations conducted for the NHANES database showed a BMI of 40 or greater for about 5% of adults [114]. Other selection criteria include a good social support system, no active substance abuse or clinically significant or unstable psychopathology, and previously demonstrated adherence to medical recommendations.

There is fair to good evidence that surgical intervention, such as gastric bypass, vertical banded gastroplasty, and adjustable banding, can produce substantial weight loss (28 to more than 40 kg). Surgical procedures result in weight loss by restricting the size of the stomach or by bypassing a portion of the intestines. Restricting the size of the stomach limits the quantity of food a patient can consume. Bypass procedures also decrease the proportion of nutrients that can be absorbed from a meal.

It is important that both healthcare providers and patients recognize that bariatric surgery is not a cure, but rather a tool. Buchwald and colleagues conducted a meta-analysis of 136 studies of bariatric surgery (conducted between 1990 and 2003), involving a total of 22,094 weight loss patients [30]. Of these patients, 19% were men and 72% were women. The mean age was 39 years (range 16 to 64 years), and the mean BMI was 46.9 (range 32.3 to 68.8 years). The objective of the analysis was to determine the impact of bariatric surgery on weight loss, operative mortality (at 30 days), and 4 obesity co-morbidities: diabetes, hyperlipidemia, hypertension, and obstructive sleep apnea. Seventy-seven percent of the patients who underwent surgery were "cured" of diabetes (as defined by discontinuation of all diabetes-related medications and maintenance of blood glucose levels within normal range), 62% had blood pressure return to normal levels, 70% saw improvements in cholesterol levels, and 86% of those suffering from sleep apnea saw the condition improve [30].

Patients lost an average 61% of their total body weight—47.5% for gastric banding, 61.6% for gastric bypass, 68.2% for gastroplasty, and 70.1% for biliopancreatic diversion or duodenal switch [30]. Operative mortality at 30 days was 0.1% for purely restrictive procedures, 0.5% for gastric bypass, and 1.1% for biliopancreatic diversion or duodenal switch. Complications included wound infection, re-operation, vitamin deficiency, diarrhea, and hemorrhaging.

Another meta-analysis, appearing the following year and looking at studies through mid-2003, concluded that bariatric surgery can be more effective than non-surgical treatment for weight loss and control of certain co-morbid conditions in people with BMI of 40 or greater. For people with lower BMI, the researchers felt that more data was needed, although surgery appeared to be superior for those with a BMI of 30 to 39 [112].

A technology assessment by the AHRQ has concluded that surgery for extremely obese patients who have tried and failed to lose weight with exercise and diet may be more effective for weight reduction [29]. The report noted that approximately 20% of patients who have weight-loss surgery experience complications. These include nutritional deficiencies, staple-line breakdown, and deep vein thrombosis. The AHRQ review also found data suggesting that weight-loss surgery may be more effective than drugs for people with BMI levels between 35 and 40. Insufficient evidence existed to assess the safety and efficacy of bariatric surgery in Medicare-eligible patients.

The Swedish Obese Subjects (SOS) study showed that gastric bypass led to a 20 kg weight loss after 8 years and reduced progression to type 2 diabetes by 81% compared with usual care [31]. The SOS study is a prospective, nonrandomized, intervention trial involving 4047 obese subjects. After an average of 10.9 years of follow-up, outcomes in a surgically treated group were compared with those in a contemporaneously matched, conventionally treated control group. No attempt was made to standardize the nonsurgical treatment, which ranged from sophisticated lifestyle intervention to no treatment at all. The primary outcome variable was overall mortality; lifestyle, diabetes, and cardiovascular risk factors were secondary endpoints. After 10 years, patients in the control group had a weight increase of 1.6% while patients in the surgical group had a 16.1% weight reduction.

Metabolic syndrome has been shown to improve or resolve following weight-loss surgery [92; 93]. In a retrospective study of patients evaluated for bariatric surgery between 1990 and 2003, metabolic syndrome was shown to improve following roux-en-Y gastric bypass surgery, with a number-needed-to-treat to resolve metabolic syndrome of 2.1 [92]. The authors concluded that weight loss was an important contributor to metabolic syndrome resolution.

INSULIN RESISTANCE

Insulin resistance is associated with an increased risk of type 2 diabetes. IFG represents a metabolic state between normal glucose homeostasis and diabetes. Patients with IGT progress to diabetes at a rate of about 6% to 10% per year; with the combination of IFG and IGT, the rate of progression may be higher [94]. The risk of cardiovascular events appears to be increased in people with IFG and IGT. IGT may have a larger effect, although more research is needed to evaluate this [94; 95].

In addition, the risk of diabetes increases in relation to BMI. According to data from the National Health Interview Survey from 1997 to 2004, for men at 18 years of age the lifetime risk of diabetes was only 7.6% if BMI was <18.5, but it was 70.3% if BMI was >35 [96]. For women, respective risks were 12.2% and 74.4%. In older adults, the change in risk with increasing BMI appears to be less steep, possibly because of overall increased risk of diabetes in this age group. At 65 years of age, the remaining lifetime risk for men ranged from 2.2% with BMI <18.5 to 34.7% with BMI >35; for women, the range was 3.7% to 36.0%. In general, the largest effect was seen in people with BMI ≥30. Moreover, increased abdominal fat mass also increases the risk of developing type 2 diabetes. The usefulness of measuring waist circumference or waist-to-hip ratio is somewhat controversial, but some studies have shown that increased risk of developing diabetes with increased abdominal girth occurs independently of BMI [33; 97].

Patients with diabetes are two to four times more likely to die from CV disease than patients without diabetes [115]. In addition, nephropathy, retinopathy, and neuropathy are well-documented chronic complications.

As noted, lifestyle intervention remains first-line therapy. The Diabetes Prevention Program (DPP) randomized 3234 patients with IFG or IGT to placebo, metformin, or intensive lifestyle (intensive nutritional and exercise counseling) changes [35].

The intensive lifestyle therapy reduced progression to type 2 diabetes nearly 60% over an average of 3 years. When overweight patients lost 7% to 10% of their body weight and took 30-minute walks 5 days a week, they decreased their risk of developing diabetes by 58%. Lifestyle intervention worked equally well in men and women, as well as in all ethnic groups, including African Americans, Asian Americans, Hispanic Americans, American Indians, and Pacific Islanders.

Metformin therapy also prevented or delayed the development of frank diabetes (31% relative reduction), although lifestyle therapy was actually more effective. Of note, metformin has not been shown to reduce the risk of CV disease in patients with metabolic syndrome, prediabetes, or diabetes, although it has reduced the incidence of diabetes-related endpoints, such as stroke [35].

Orchard and colleagues studied 3234 patients who were part of the DPP to determine whether diet and exercise or metformin prevents or reverses metabolic syndrome in patients with IGT [55]. As discussed, patients with prediabetes were randomly assigned to diet and exercise, metformin, or neither. The interventions consisted of metformin 850 mg twice daily or intensive lifestyle changes consisting of 150 minutes of exercise per week. Patients were followed for an average of 3.2 years from June 1996 through July 2001.

NCEP ATP III criteria were used for the definition of metabolic syndrome. At baseline, 53% of patients met the criteria for metabolic syndrome. At the conclusion of the study, incidence of metabolic syndrome was reduced by 41% in the lifestyle group and by 17% in the metformin group, compared with placebo. Three-year incidences were 40% for placebo, 33% for metformin, and 27% for lifestyle group. For those patients who had the syndrome at the beginning of the study, more were likely to be free of it at the end of the study if they received lifestyle intervention or metformin rather than placebo. Eighteen percent of the placebo group, 23% of the metformin group, and 38% of the lifestyle group no longer had metabolic syndrome. Overall, although both interventions were beneficial, the benefit of the lifestyle intervention was larger than the benefit of metformin [55].

In the Finnish Diabetes Prevention Study, 522 middle-aged obese patients with IGT were randomized to receive either brief diet and exercise counseling or intensive individualized instruction on weight reduction, food intake, and physical activity [36]. After a mean follow-up of 3.2 years, there was a 58% relative reduction in the incidence of diabetes in the group receiving intensive individualized instruction compared to the control group. A later report showed that lifestyle changes were sustained in many patients even after the intervention ended [116]. The active intervention period lasted an average of 4 years, and patients were followed for a median of 7 years total. During the total follow-up, the risk of type 2 diabetes incidence was reduced by 43% in the intervention group compared to the controls.

A 2008 Chinese study offers 20 years of follow-up for a lifestyle intervention in patients with IGT [117]. Patients in this study were randomly assigned to diet, exercise, diet plus exercise, or a control group. Active intervention was offered for the first 6 years, from 1986 to 1992. Patients were re-evaluated in 2006. Over the 20-year period, patients in the lifestyle intervention groups had a 43% lower incidence of diabetes, controlled for age and clustering by site.

With respect to pharmacotherapy, some medications have been shown to improve insulin resistance and delay progression to diabetes. In the DPP, patients using metformin showed a 31% decrease in type 2 diabetes at 3 years. A 2008 meta-analysis concluded that, in people at risk for diabetes, metformin improves weight, lipid profiles, and insulin resistance, with a reduction in new-onset diabetes of 40% during a mean duration of 1.8 years [118]. In the Troglitazone in Prevention of Diabetes (TRIPOD) study, troglitazone reduced progression from gestational diabetes to type 2 diabetes by 55% [37]. However, it should be noted that troglitazone was removed from U.S. markets in 2000 by its manufacturer due to reports of hepatic failures and deaths associated with its use [67]. Rosiglitazone and pioglitazone have also shown some efficacy in delaying or preventing diabetes, possibly by helping to preserve beta-cell function in addition to insulin sensitization [119; 120]. In the Study to Prevent Non-Insulin Dependent Diabetes Mellitus (STOP-NIDDM), 1429 patients with IGT were randomized to receive either acarbose or placebo [38]. After a mean follow-up of 3.3 years, acarbose reduced progression to type 2 diabetes by 25%.

Healthcare professionals should understand that there are benefits of multifactorial intervention in patients with multiple metabolic abnormalities. For instance, in the Steno-2 trial, 160 patients with type 2 diabetes and microalbuminuria received intensive therapy, consisting of a reduced-fat diet, regular exercise, and smoking cessation counseling if applicable, and were prescribed an angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) regardless of blood pressure [39]. They also received vitamin supplementation and aspirin and were prescribed antidiabetic medications as well as lipid treatment with a statin and/or fibrate. At the conclusion of the study, participants who received intensive therapy had a 53% reduction of macrovascular disease, which was greater than the effects reported in single intervention trials of ACE inhibitors, statins, or blood pressure medications.

Keep in mind that drug therapy for insulin resistance is not approved for patients without diabetes. For the most part, the ADA does not recommend pharmacologic treatment of IFG or IGT to prevent type 2 diabetes. However, they do state that metformin may be considered for patients who have a BMI of 35 or greater, are younger than 60 years of age, and have both IGF and IGT plus other risk factors [130].

DYSLIPIDEMIA

As noted, the dyslipidemia in metabolic syndrome is characterized by elevated triglyceride (greater than 150 mg/dL), low HDL (less than 40 mg/dL in men; less than 50 mg/dL in women), and small, dense LDL cholesterol. The diagnosis of dyslipidemia is best made when a patient does not have any acute illness. HDL and LDL levels are not significantly altered by food, but triglyceride levels can rise substantially after food intake. The current recommendation for testing requires a 9- to 12-hour fast prior to laboratory measurements. There are some conditions that can cause similar dyslipidemia, particularly low HDL, characteristic of metabolic syndrome. These include glucocorticoid excess as well as hypothyroidism; although relatively uncommon, healthcare providers should be aware of them.

EVIDENCE-BASED PRACTICE RECOMMENDATION

The National Cholesterol Education Program Adult Treatment Panel III recommends that a fasting lipoprotein profile be obtained once every five years for all adults 20 years of age or older.

(http://www.guideline.gov/summary/summary.aspx?doc_id=5503. Last accessed October 16, 2008.)

Level of Evidence: Consensus Statement/Expert Opinion

Since the NCEP ATP III published guidelines at the end of 2002, numerous additional trials relating to various therapies have been published. As a result, NCEP issued interim guidelines as an addendum to the ATP III guidelines regarding the management of cholesterol, which can be accessed at http://circ.ahajournals.org/cgi/content/full/110/2/227.

When addressing dyslipidemia, physicians should first target LDL levels that are greater than 100 mg/dL. The ATP III makes the following ranked recommendations for patients with metabolic syndrome and atherogenic dyslipidemia [60]:

1. Treat LDL cholesterol first
2. For those patients with triglyceride greater than 200 mg/dL, calculate the non-HDL cholesterol level (total cholesterol – HDL cholesterol):
    a. Non-HDL cholesterol goal = LDL cholesterol goal + 30 mg/dL

Lowering LDL is critical as it is primarily elevated LDL cholesterol that is associated with coronary artery disease. In high-risk patients, an LDL cholesterol level goal of less than 70 mg/dL is a therapeutic option. Ideally, HDL for men should be at least 35 mg/dL and at least 40 mg/dL for women.

Treatment begins with lifestyle changes (diet and exercise). In high-risk patients, if the LDL cholesterol is at least 100 mg/dL, use of an LDL-lowering medication is indicated simultaneously with lifestyle changes. Several studies have demonstrated the benefit of lifestyle changes in managing dyslipidemia. For instance, Stefanick and colleagues randomized 197 men and 180 postmenopausal women with high LDL and low HDL to aerobic exercise, diet, diet and exercise, or no treatment [40]. At the end of the study, there was significant reduction in LDL in the diet plus exercise group compared with diet alone or the control group. For those patients who do not reach the goal with diet and exercise, treatment with a cholesterol-lowering agent, most often a statin, is beneficial. However, keep in mind that some statins do not correct abnormalities of triglyceride and HDL.

After the LDL goal is obtained, non-HDL cholesterol becomes the focus. If the non-HDL cholesterol remains elevated, ATP III suggests either increasing the dose of the statin or combination therapy [122]. Combination therapy typically involves a statin and a triglyceride-lowering drug, such as a fibrate (e.g., gemfibrozil or fenofibrate) or niacin. The fibrates typically lower triglyceride levels by 20% to 50% and raise HDL cholesterol by 10% to 35% [122]. One cautionary note: fibrates can increase the risk of myopathy from statins.

Niacin is one of the most effective drugs to raise HDL cholesterol and lower triglyceride. However, it has been associated with insulin resistance, particularly in patients with diabetes. The Arterial Disease Multiple Interventions Trial (ADMIT) evaluated niacin therapy in 486 patients with peripheral vascular disease, including 125 patients with diabetes for a period of 1 year [41]. Niacin increased glucose levels by 8.1 mg/dL in the diabetic patients, compared with an increase of 6.3 mg/dL in the nondiabetic subjects. The Assessment of Diabetes Control and the Evaluation of the Efficacy of Niaspan Trial (ADVENT) randomized 148 type 2 diabetic patients to placebo or extended-release niacin [42]. Dose-dependent increases in HDL cholesterol and decreases in fasting triglyceride occurred with extended-release niacin. These changes were accompanied by an increase in glycosylated hemoglobin, from 7.2% to 7.4%. The HDL Atherosclerosis Intervention Trial (HATS) investigated the effects of combined therapy with simvastatin and niacin in patients with coronary artery disease and low HDL levels [43]. Combined therapy resulted in fewer cardiac events. In addition, glycemic control was less tight in the simvastatin-niacin group only during the initial few months. After 8 months, the glucose levels returned to pretreatment levels and remained stable for the remainder of the study. Of note, the ADA does support the judicious use of niacin (less than 2 g/day) for increasing HDL cholesterol, lowering triglycerides, and improving LDL [121].

HYPERTENSION

Hypertension remains a significant cause of morbidity and mortality. Twenty-nine percent of U.S. adults have hypertension, yet only 68% of them are currently being treated. Furthermore, only 78% of people with hypertension are aware that they have the condition [123]. This is especially concerning because every 20/10 mm Hg increase in blood pressure doubles the risk of cardiac disease. Antihypertensive therapy has been associated with significant risk reductions, including a nearly 40% reduction in stroke and a 25% reduction in myo-

JNC 7 CLASSIFICATION OF BLOOD PRESSURE FOR ADULTS		
Blood Pressure Classification	**Systolic Blood Pressure**	**Diastolic Blood Pressure**
Normal	<120 mm Hg	<80 mm Hg
Prehypertension	120–139 mm Hg	80–89 mm Hg
Stage 1 hypertension	140–159 mm Hg	90–99 mm Hg
Stage 2 hypertension	≥160 mm Hg	≥100 mm Hg
Source: [46]		*Table 2*

cardial infarction. The changes in blood pressure do not have to be dramatic to ascribe benefit. Each 2 mm Hg reduction in systolic blood pressure produces a 7% reduction in a patient's risk of ischemic heart disease mortality and a 10% reduction in the risk of fatal stroke [45].

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) introduced a category of "prehypertension" to recognize that underlying risk factors raise blood pressure to ranges that increase a patient's risk for CV disease ***(Table 2)*** [46]. Prehypertension includes people with a systolic blood pressure of 120–139 mm Hg or a diastolic blood pressure of 80–89 mm Hg. Keep in mind that ATP III includes a blood pressure of 130/85 mm Hg or greater as a risk factor for metabolic syndrome. JNC 7 recommends antihypertensive drugs in all patients with blood pressures greater than 140/90 mm Hg and all diabetic patients with blood pressures greater than 130/80 mm Hg.

Patients with either prehypertension or stage 1 hypertension should initially be treated with lifestyle modifications. Exercise has been demonstrated to reduce hyperinsulinemic responses to glucose challenges in patients with metabolic syndrome [47]. Watkins and colleagues evaluated the effects of a 6-month intervention involving either aerobic exercise training alone or exercise combined with a structured weight-loss program on cardiovascular risk factors associated with metabolic syndrome. A total of 53 men and women who showed the hyperinsulinemia, dyslipidemia, and high blood pressure characteristic of metabolic syndrome were randomly assigned to an exercise-only group, an exercise and weight loss group, or a control group. Before and following treatment, participants underwent measurement of glucose tolerance, lipid levels, and clinical blood pressure. At the end of the study, hyperinsulinemic responses to the glucose challenge test were significantly reduced in both exercise groups. Participants who showed the largest amount of weight loss showed the most robust improvements in abnormal insulin responses. Diastolic blood pressure was significantly reduced in the exercise and weight loss group but not in the exercise-only group. Lipid profile was not significantly improved by either intervention. These results suggest that exercise is an effective treatment for hyperinsulinemia and lowering of diastolic blood pressure in patients with metabolic syndrome.

In 2003, a meta-analysis of 54 controlled trials examined the effects of aerobic exercise on systolic and diastolic blood pressure [48]. Aerobic exercise was associated with a significant reduction in mean systolic and diastolic blood pressure. A reduction in blood pressure was associated with aerobic exercise in hypertensive participants and normotensive participants and in overweight participants and normal-weight participants. The authors concluded that aerobic exercise reduces blood pressure in both hypertensive and normotensive persons. A meta-analysis of trials between 1998 and 2006 found statistically significant reductions in systolic blood pressure with each of several lifestyle interventions, including improved diet (5.0 mm Hg), aerobic exercise (4.6 mm Hg), alcohol restriction (3.8 mm Hg), sodium restriction (3.6 mm Hg), and fish oil supplements (2.3 mm Hg) [124].

Along with exercise and the previous advice given about nutrition, healthcare providers may wish to consider the Dietary Approach to Stop Hypertension (DASH) diet. The DASH diet is rich in fruits, vegetables, nuts, and low-fat dairy products and low in saturated fat, sugar, cholesterol, and refined carbohydrates. It includes about 3000 mg of sodium a day [49]. Numerous studies have shown the DASH diet to lower blood pressure [50; 51; 52]. In addition, increasing the intake of fiber in the typical Western diet may contribute to the prevention of hypertension [53].

If blood pressure remains high, pharmacotherapy should be considered. Because endothelial dysfunction appears to be present in many patients with metabolic syndrome, ACE inhibitors and ARBs are useful in improving hypertension as well as mitigating the endothelial damage. Furthermore, ACE inhibitors may be particularly useful in patients with diabetes, as they protect against renal disease [131]. ARBs may have similar effects. The Losartan Intervention for Endpoint (LIFE) trial demonstrated lower rates of nonfatal and fatal CV disease in diabetic, hypertensive patients with left ventricular hypertrophy who took the ARB losartan compared to those that took atenolol, a beta-blocker [54]. Losartan was also more effective than atenolol in reducing all-cause mortality.

JNC 7 recommends a thiazide-type diuretic as initial therapy for most patients with stage 1 hypertension [46]. Healthcare professionals treating patients with metabolic syndrome should be aware that thiazides have been associated with insulin resistance and other metabolic changes. However, at lower doses, changes in glucose levels appear to be small [125].

As noted earlier, Mr. G is on a thiazide for blood pressure control. Because his blood pressure is well controlled, this medication was not changed. Instead, the focus was to concentrate on lifestyle intervention (nutrition/physical activity) and re-evaluate in 6 to 8 weeks.

CONCLUSION

Metabolic syndrome is a cluster of metabolic abnormalities that typically includes some combination of abdominal obesity, insulin resistance, hypertension, dyslipidemia, and a prothrombic state. As reviewed, these abnormalities lead to an increased risk of CV disease and diabetes. The underlying pathophysiology of metabolic syndrome remains to be determined; however, poor nutritional intake and sedentary lifestyle have contributed to its increased prevalence. Therapeutic lifestyle interventions are the first-line therapy. Pharmacologic agents can be considered to help control the risk factors.

RESOURCES

How to Understand and Use the Nutrition Facts Label
http://www.cfsan.fda.gov/~dms/foodlab.html

American Diabetes Association
http://www.diabetes.org

National Institutes of Health
http://www.nlm.nih.gov/medlineplus/metabolicsyndromex.html

American Heart Association
http://www.americanheart.org

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