Metabolic Syndrome: A Growing Epidemic

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- Complete the questions at the end of the course.
- Return your completed Evaluation to NetCE by mail or fax, or complete online at www.NetCE.com. (If you are a physician or Florida nurse, please return the included Answer Sheet/Evaluation.) Your postmark or facsimile date will be used as your completion date.
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Faculty

John J. Whyte, MD, MPH, is currently the Chief Medical Officer at WebMD. In this role, he leads efforts to develop and expand strategic partnerships that create meaningful change around important and timely public health issues. Previously, Dr. Whyte was the Director of Professional Affairs and Stakeholder Engagement at the FDA's Center for Drug Evaluation and Research and the Chief Medical Expert and Vice President, Health and Medical Education at Discovery Channel, part of the media conglomerate Discovery Communications.

Prior to this, Dr. Whyte was in the Immediate Office of the Director at the Agency for Healthcare Research Quality. He served as Medical Advisor/Director of the Council on Private Sector Initiatives to Improve the Safety, Security, and Quality of Healthcare. Prior to this assignment, Dr. Whyte was the Acting Director, Division of Medical Items and Devices in the Coverage and Analysis Group in the Centers for Medicare & Medicaid Services (CMS). CMS is the federal agency responsible for administering the Medicare and Medicaid programs. In his role at CMS, Dr.Whyte made recommendations as to whether or not the Medicare program should pay for certain procedures, equipment, or services. His division was responsible for durable medical equipment, orthotics/prosthetics, drugs/biologics/therapeutics, medical items, laboratory tests, and non-implantable devices. As Division Director as well as Medical Officer/Senior Advisor, Dr. Whyte was responsible for more national coverage decisions than any other CMS staff.

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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 Planners/Director Disclosure

The division planners and director have disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Audience

This course is designed for healthcare professionals working with adults or adolescent patients who exhibit risk factors for metabolic syndrome.

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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 healthcare professionals about the epidemiology and treatment of metabolic syndrome so they may better care for their patients.

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 United States, based on age, sex, race, and other factors.
3. Evaluate risk factors of metabolic syndrome.
4. Utilize screening tools to diagnose metabolic syndrome.
5. Offer current dietary recommendations.
6. Identify the current physical activity recommendations.
7. Consider pharmaceutical interventions currently available for obesity.
8. Recognize circumstances when surgery should be considered as a treatment option for obesity.
9. Define dyslipidemia and its treatment recommendations.
10. Evaluate hypertension and its treatment modalities.

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 disease, type 2 diabetes, and stroke. It was first described in 1988 and has been referred to by a variety of names, including "Reaven syndrome," "deadly quartet," "syndrome X," "insulin resistance syndrome," and "dysmetabolic syndrome" [1; 2]. In general, the components include central adiposity, hypertension, dyslipidemia, insulin resistance, a proinflammatory state, and a prothrombotic state [3; 4]. 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 [3; 4].

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) [5]. 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 [5]. The American Heart Association (AHA), in their statement on the diagnosis and management of 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 [6].

As an aside, in 2013 the National Heart, Lung, and Blood Institute (NHLBI) discontinued its publication of clinical practice guidelines, instead choosing to provide its systemic evidence reviews to professional organizations, who will then publish guidelines based on these and other findings [7]. This change affected five cardiovascular disease-related documents that were in the process of being crafted, including those addressing cholesterol, blood pressure, risk assessment, lifestyle interventions, and obesity. Throughout this course, this change is noted as appropriate.

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 man, 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 longstanding. 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***) [8]. 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, 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 [9]. In this review, they determined that lowering the glucose cutoff more effectively identified men at high risk of diabetes and coronary artery disease.

NCEP ATP III CLINICAL IDENTIFICATION OF METABOLIC SYNDROME[a]	
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 (HDL) cholesterol	Men: <40 mg/dL Women: <50 mg/dL
Blood pressure	≥130/≥85 mm Hg
Fasting glucose	≥110 mg/dL
[a]Defined by the presence of three or more of the listed components	
Source: [8; 9]	*Table 1*

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 two or more risk factors. 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 [9].

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 [9]. The WHO criteria differ from the ATP III criteria in that they require the presence of insulin resistance as part of the diagnosis. In addition, the WHO criteria use different diastolic 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 [9]:

- 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 two of the following in order to be diagnosed with metabolic syndrome [9]:

- 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 and/or waist:hip ratio >0.9 in men, >0.85 in women
- Urinary albumin excretion rate ≥20 mcg/min or albumin:creatinine ratio ≥30 mg/g

AMERICAN COLLEGE OF ENDOCRINOLOGY PANEL

The American College of Endocrinology (ACE) has 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 these criteria [10; 11]:

- 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 two-hour post-glucose challenge.

THE INTERNATIONAL DIABETES FEDERATION

The International Diabetes Federation (IDF) offers yet another definition of the metabolic syndrome [12]. Its criteria 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 IDF 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 [12]. Metabolic syndrome is diagnosed when this sign is positive in addition to any two of the following four factors [12]:

- Elevated triglyceride level (≥150 mg/dL) or specific treatment for this lipid abnormality
- Reduced HDL cholesterol (<40 mg/dL in men or <50 mg/dL in women) 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.

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 34% of adults in the United States have metabolic syndrome. This represents more than one in three adults older than 18 years of age and more than half (51%) of adults 60 years of age and older [13; 14].

SEX/RACE

Among non-Hispanic White individuals, the age-adjusted prevalence for metabolic syndrome is 35% among men and 36% among women. Minority populations are disproportionately affected; however, the prevalence of metabolic syndrome varies for men and women. Prevalence in non-Hispanic Black women is 34%; prevalence in non-Hispanic Black men is 27%. Mexican American women have a prevalence that is slightly higher (31%) than in Mexican American men (27.5%) [14].

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 41.9% of the adult population is obese, and 9.2% are severely obese. Approximately 19.7% of children and adolescents are considered obese [15; 16].

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 [17].

Obesity costs alone are estimated to be at least $173 billion annually [18]. Total medical expenditures attributable to diabetes are estimated at $327 billion, with $237 billion in direct medical expenditures and $90 billion for indirect expenditures (e.g., disability, work loss, premature mortality) [19; 20]. 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 [21]. Some evidence shows increased cortisol to cause insulin resistance. Insulin resistance causes microvascular damage, which predisposes a patient to endothelial dysfunction, vascular resistance, hypertension, and vessel wall inflammation [22]. Accumulated effects of endothelial dysfunction and hypertension can further result in ischemic heart disease [22]. Hypertension increases vascular resistance and stiffness, causing peripheral vascular disease and structural heart disease (e.g., left ventricular hypertrophy, cardiomyopathy), leading to renal impairment [22]. 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 [23].

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 [24; 25].

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 65% of obese men and 56% of obese women, compared with 6.8% of men and 9.3% of women who are underweight and normal weight [13].

One apparent foundation of metabolic syndrome is excess deposition of adipose tissue, which may give rise to an insulin resistant state [22]. Adipose tissue is now recognized not only as a main site of storage of excess energy derived from food intake but also as an endocrine organ [26]. Adipose tissue secretes leptin, tumor necrosis factor, and free-fatty acids that diminish the effects of insulin. In addition, leptin impairs insulin release by pancreatic beta cells [27]. 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 [22; 26].

Of note, accumulation of intra-abdominal fat, irrespective of whether a person is overweight, may result in insulin resistance and contribute to metabolic syndrome [28]. 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 cardiovascular 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 obesity-related metabolic diseases, including diabetes [26]. A study was published that compared BMI, waist circumference, and waist-to-hip ratio in predicting the development of type 2 diabetes [29]. 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 (i.e., <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 [29]. In another study, researchers 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 [30]. 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 adipose tissue, on the other hand, did not predict diabetes.

The American Medical Association (AMA) recently adopted a new policy that recognizes the issues with BMI measurement (e.g., historical harm, no consideration of gender/ethnicity) and suggests that it be used in conjunction with other valid measures of risk, including but not limited to [31]:

- Visceral fat
- Body adiposity index
- Body composition
- Relative fat mass
- Waist circumference
- Genetic or metabolic factors

The newly adopted AMA policy also recognizes that [31]:

- BMI is significantly correlated with the amount of fat mass in the general population but loses predictability when applied on an individual level.
- Relative body shape and composition heterogeneity across race and ethnic groups, sexes, genders, and age-span are essential to consider when applying BMI as a measure of adiposity.
- BMI should not be the sole criterion used to deny appropriate insurance reimbursement.

The AMA also modified existing policy on the clinical utility of measuring BMI, body composition, adiposity, and waist circumference to support greater emphasis on education about the risk differences within and between demographic groups.

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 regulates 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 [32; 33].

Studies have shown that insulin-secretory ability predicts the risk of developing type 2 diabetes, with a three-fold increase in risk in persons with low insulin secretion and a five-fold increase in persons with insulin resistance [34]. Participants in the San Antonio Heart Study were evaluated for insulin resistance and insulin secretion [35]. The researchers tested fasting plasma glucose and then performed oral glucose tolerance tests in 1,282 patients who were non-diabetic (i.e., 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 eight 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 [36]. 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. Many other large-scale clinical trials and meta-analyses have reported that the presence of metabolic syndrome is highly predictive of new-onset type 2 diabetes in many different populations [37]. The authors of one study compared the degree

of severity of metabolic syndrome and risk of type 2 diabetes conferred by the individual components of metabolic syndrome (ATP III score) with that conferred by the use of a sex- and race-specific continuous metabolic syndrome severity score to predict risk of diabetes [38]. The study included more than 13,000 participants followed up over a median of 7.8 years. The authors found that the use of a sex- and race-specific metabolic syndrome severity score provided an additional prediction of risk of diabetes beyond that predicted solely by the individual components of metabolic syndrome, with a greater risk for Black participants than White participants [38].

METABOLIC SYNDROME AND CARDIAC RISK

Cardiovascular disease remains a common cause of death in both men and women in the United States, precipitating one of every three deaths [39]. Metabolic syndrome significantly increases the risk of cardiovascular 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 cardiovascular risk factors, making it a potentially useful composite of its component parts [35; 40; 41]. 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 [42]. 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%. Each component of metabolic syndrome is an independent risk factor for cardiovascular disease and the combination of these risk factors elevates rates and severity of cardiovascular disease related to a spectrum of cardiovascular conditions, including microvascular dysfunction, coronary atherosclerosis and calcification, cardiac dysfunction, myocardial infarction, and heart failure [43].

A review of the National Health and Nutrition Examination Survey (NHANES) data revealed that in patients younger than 50 years of age, the age-adjusted prevalence of cardiovascular 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%) [44]. The prevalence of cardiovascular 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 1,200 men without cardiovascular 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 [45]. 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 [46].

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 cardiovascular disease event (i.e., coronary heart disease [CHD], congestive heart failure, or stroke) over a median of 11 years of follow-up [47]. Regarding cardiovascular 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 cardiovascular mortality better than metabolic syndrome [48].

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 cardiovascular 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 [49]. A 2005 report using data from a 20-year prospective study of 5,128 men, found that the Framingham Risk Score was a more sensitive predictor of coronary heart disease at both 10- and 20-year follow-up [50; 51]. 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. Studies have confirmed that metabolic syndrome increases the risk of cardiovascular disease, with relative risks from 1.53 to 2.18 [52; 53; 54; 55; 56].

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 [9; 57; 58; 59; 60; 61; 62]. Psychological characteristics (e.g., anger, depression, hostility) may also be linked to increased risk for metabolic syndrome, although psychological disorders, particularly anxiety, may represent comorbidity or a complication of metabolic syndrome [23; 63; 64]. Results of studies of migrants in Europe and North America suggest that susceptibility to metabolic syndrome is predominantly due to environmental factors and psychological stress [65]. Acculturation contributes to the emergence of cardiovascular risk factors in first-generation adult immigrants, while increased risk for later development of hypertension and dyslipidemia has been detected in adolescent immigrants [65].

DIAGNOSIS/SCREENING

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 should include a thorough discussion of past medical conditions as well as current risk factors.

Evaluation of patients for metabolic syndrome should include measurement of [6]:

- 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 [6]. The lipid profile includes total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides. 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 [8; 66]. 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 [67]. The recommendation for aspirin prophylaxis was eliminated in the 2019 Endocrine Society guideline [68].

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

(BMI may be used to help 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 in pounds] divided by [height in 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 triglycerides, 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 may 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 of 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 cardiovascular disease. Therefore, the first step in treatment is effective lifestyle interventions, focusing on nutrition and exercise.

The USPSTF recommends offering or referring adults with cardiovascular disease risk factors to behavioral counseling interventions to promote a healthy diet and physical activity.

(https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/healthy-diet-and-physical-activity-counseling-adults-with-high-risk-of-cvd. Last accessed October 10, 2023.)

Strength of Recommendation: B (The USPSTF recommends the service, as there is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.)

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 should 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 with moderate certainty that medium- or high-intensity primary care behavioral counseling interventions to promote a healthful diet and physical activity have a small net benefit in adult patients without cardiovascular disease, hypertension, hyperlipidemia, or diabetes, but no consistent benefit on all-cause or cardiovascular mortality or morbidity [69]. 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 but that clinicians should consider patient readiness for change, social support and community resources that support behavioral change, and other healthcare and preventive service priorities to avoid lost opportunities to provide other healthcare services that offer a greater health effect [69]. Assessing dietary patterns and recommending change is critical for success.

Reduction in Calories

One of the most important components relating to nutritional advice for patients who are overweight 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 2,000 calories. As a quick rule of thumb, patients can calculate the number of daily calories they require by multiplying their current weight in pounds by 13 (or 15 if one is active). Patients who are overweight should reduce the number of consumed calories in order to lose weight. Reduction in calories is the most important dietary component of weight loss.

Between 2007 and 2008 in the United States, the 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 [70]. Between 2007 and 2008, women consumed 1,771 calories per day on average. Men's caloric intake was 2,504 calories per day over the same period. Energy intake appeared relatively stable over the 10-year period from 1999 to 2008 [70]. A look at NHANES data up to 2002 found that Americans have been consuming both increasingly larger amounts of food and more energy-dense foods than in earlier years [71]. On average, U.S. residents were 25 pounds 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 pounds from 140.2 pounds during the same period [72]. NHANES data from 2013–2014 indicates that less than one-third of U.S. adults maintain a healthy weight [73]. This is largely due to an increase in daily calorie consumption. NHANES data from 2009–2010 found that Americans snacked more between lunch and dinner and often snacked in place of meals [74].

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 500–750 daily [75]. This reduction will produce the recommended weight loss of 1–2 pounds per week in most patients.

Portion control is also a key to weight loss. Portion control has been shown to produce 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 [76]. 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 [77]. (Note: The food guide pyramid has been replaced with the MyPlate model [78].)

Dietary Reference Values

Since the 1990s, the Institute of Medicine (IOM) has issued a series of reports that suggests 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 [79]:

- 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 nutritional 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. Additionally, a meta-analysis and systematic review of long-term studies of low-fat, high-protein diets found no net benefit on outcome markers of obesity, cardiovascular disease, or glycemic control [80].

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 [81]. 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 one 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 one year, irrespective of diet. However, by one 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 (lifestyle, exercise, attitudes, relationships, and nutrition) diets in overweight and obese women [82]. Women on the Atkins diet lost the most weight (i.e., 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.

In yet another study, researchers randomized 132 patients with a BMI greater than 35 to either a low-carbohydrate diet (i.e., less than 30 g/d) or a low-fat diet (i.e., less than 30% calories from fat) [83]. Although the low-carbohydrate group lost more fat at six months, both groups had the same weight loss at one year (i.e., 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.

Intermittent fasting and time-restricted feeding are also being investigated for their potential in regulating and improving chronic health conditions and disorders, including cardiovascular disease [84; 85; 86].

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

Dietary Guidelines

In 2020, the U.S. Department of Health and Human Services in conjunction with the U.S. Department of Agriculture issued the ninth edition of the Dietary Guidelines for Americans [87]. The guidelines have been revised and published every five years since 1980. A rigorous process, using 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 of previous guidelines was on individual dietary components, such as food groups and nutrients. The focus of the 2020 edition is on overall eating patterns and their food and nutrient characteristics, with guidance for choosing a healthy diet to prevent diet-related chronic disease. The underlying premise is that nutritional needs should be met primarily from foods. The 2020 edition also includes data that describe the significant differences between Americans' consumption patterns and guideline recommendations and indicate where shifts are needed to help people achieve healthy eating patterns. One such shift is choosing nutrient-dense foods and beverages in place of less healthy choices, rather than increasing overall intake [87].

The 2020 guidelines provide four key recommendations that encourage healthy eating patterns. These recommendations should be applied in their entirety due to the interconnected relationship that each component can have with others [87]:

- Follow a healthy eating pattern across the lifespan. Food and beverage choices matter. Make selections that promote a healthy body weight, support adequate nutrition, and reduce risk of chronic disease.
- Customize and enjoy nutrient-dense food and beverage choices to reflect personal preferences, cultural traditions, and budgetary considerations. A healthy dietary pattern can benefit all individuals regardless of age, race, or ethnicity, or current health status.
- Focus on meeting food group needs with nutrient-dense foods and beverages, and stay within calorie limits. Nutrient dense foods are those that provide adequate nutrient intake and/or positive health effects and that have not been "diluted" by the addition of calories from added solid fats, sugars, or refined starches not naturally present in the food.
- Limit foods and beverages higher in added sugars, saturated fat, and sodium, and limit alcoholic beverages.

Overall, a healthy eating plan is one that emphasizes a variety of vegetables from all subgroups, whole fruits, whole grains, fat-free or low-fat dairy products and/or fortified soy beverages, lean meats, poultry, fish, seafood, beans, eggs, unsalted seeds and nuts, soy products, and oils [87]. In addition, the plan should be low in saturated fats, trans fats, cholesterol, sodium, and added sugars.

The following quantitative recommendations were made for components of the diet that should be limited as they are of particular public health concern in the United States [87]:

- Consume less than 10% of calories per day from added sugars.
- Consume less than 10% of calories per day from saturated fats.
- Consume less than 2,300 mg of sodium (approximately one teaspoon of salt) daily.
- If alcohol is consumed, limit it to no more than one drink per day for women and up to two drinks per day for men, and only by adults of legal drinking age.

To further promote health and reduce the risk of chronic disease, Americans of all ages should meet the physical activity guidelines published by the U.S. Department of Health and Human Services and should aim to achieve and maintain a healthy body weight [88].

With respect to children, those 2 to 3 years of age should consume 2 cups daily of fat-free or low-fat milk; those 4 to 8 years of age should consume 2½ cups daily; and children and adolescents 9 to 18 years of age should consume 3 cups of milk daily [87]. 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 has issued a dietary model called MyPlate [78; 87]. The MyPlate model 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. It encourages consumers to take action by balancing calories, using portion control, increasing consumption of healthy foods, and reducing consumption of unhealthy foods and food components. Patients should be encouraged to view the MyPlate website (***Resources***) to view sample menus and recipes and develop a personalized plan.

Currently, Mr. G snacks on 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 about the food he eats. Either the physician can provide some basic dietary information, or the patient can be referred to a dietitian. The goals of dietary counseling for Mr. G would be:

- *Mr. G first should understand roughly how many calories he is consuming per day. His goal should be to consume no more than 2,000 calories per day. He may wish to keep a food log for two to three 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 three 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 on food high in sugar, sodium, and added fat and substitute these for nutrient-dense food/beverage choices. Because he consumes a fair amount of soda, simply eliminating one can of soda per day could lead to a 5- to 10-pound weight loss over the course of a year. The emphasis should be on gradual lifestyle changes that are sustainable and acceptable to Mr. G.*

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. However, over the last four decades, numerous surveys and cohort studies have consistently reported that Western societies are significantly less physically active than past generations [89; 90; 91; 92]. Additionally, a growing number of studies have reported that higher cardiorespiratory fitness is inversely related to the development of metabolic syndrome [93; 94].

According to the U.S. Department of Health and Human Services, strong scientific evidence shows that physical activity delays death from all causes. This includes the leading causes of death, such as heart disease and some cancers, as well as other causes of death.

(https://health.gov/sites/default/files/2019-09/Physical_Activity_Guidelines_2nd_edition.pdf. Last accessed October 10, 2023.)

Level of Evidence: Consensus Statement/Expert Opinion

When discussing exercise, it is important to focus on frequency (i.e., 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 [95]. The AHA recommends either 30 minutes of moderate physical activity five days per week or 20 minutes of vigorous activity three or more days per week and also suggests that resistance training or other strengthening activities be performed on two or more nonconsecutive days each week [96].

According to the IOM, adults should set a long-term goal of at least 60 minutes of moderate-intensity physical activity on at least five days of the week [79]. This is an increase from 30 minutes recommended by the U.S. Surgeon General. Recommendations described in the U.S. Dietary Guidelines suggest the following [87]:

- 60 minutes or more of physical activity daily for children 6 to 17 years of age. Most should be moderate- or vigorous-intensity aerobic activity and should include vigorous-intensity, muscle-strengthening, and bone-strengthening activity at least three days of the week.
- At least 150 minutes per week of moderate-intensity activity or 75 minutes per week of vigorous-intensity aerobic physical activity, or an equivalent combination for adults 18 to 64 years of age. Aerobic activity should be performed in episodes of at least 10 minutes and, if possible, spread throughout the week. Adults should also include muscle-strengthening activities two or more days/week.
- Adults 65 years of age and older should follow the adult guidelines whenever possible with an emphasis on maintaining/improving balance if at risk of falling.

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. AHA recommendations provide 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 of exercise per week [96].

The following advice regarding exercise may be given to patients:

- **Plan to exercise a minimum of three days per week.** Patients can slowly add days as they become more comfortable. The goal should be to exercise five days per 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 per 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 should 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. Researchers studied 906 women who were being evaluated for coronary artery disease [97]. They 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. A 15-year study was conducted of 4,400 patients who were given a treadmill test between the ages of 18 and 30 years as part of the Coronary Artery Risk Development in Young Adults (CARDIA) study [98]. 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.

The observational cohort study design was used to calculate all-cause death rates in men with diabetes across quartiles of fitness and BMI categories. Study participants were 2,196 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 [99]. 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 [100].

A study of 15,466 healthy men and 3,757 men with metabolic syndrome was conducted over a 10-year period to determine the relationship between cardiorespiratory fitness and mortality [101]. Compared with the healthy subjects, men with metabolic syndrome had twice the risk of dying from cardiovascular 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 7,000 women, researchers examined the prevalence of metabolic syndrome across age strata and cardiorespiratory fitness levels and found that "the prevalence of metabolic syndrome was markedly lower across progressively higher levels of fitness in women of different age groups" [102]. 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, which is 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. Researchers 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 (VO2 max) during a bicycle exercise test and the presence of metabolic syndrome [103]. Adjusting for BMI weakened the association but did not eliminate it, although adjusting for waist circumference made the association non-significant in men. The researchers later additionally found that higher levels of cardiorespiratory fitness may protect against metabolic syndrome and help resolve it in older individuals [104]. Data was examined from the Second Manifestations of ARTerial disease (SMART) study, an ongoing cohort study of patients with cardiovascular disease or risk factors [105]. Looking at patients who already had evidence of cardiovascular disease, the researchers 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 9,007 men and 1,491 women who were initially free of metabolic syndrome, researchers demonstrated that low cardiovascular fitness may predict development of the syndrome [106]. 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 nonsignificant trend for women [106].

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 level improved dramatically [107].

As noted, weight reduction of as little as 5% body weight (often as little as 5–10 pounds) is associated with lower incidence of diabetes, reduced blood pressure, and improved dyslipidemia [108].

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 three days per 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, five days of the week. A program of interest to some patients is the 10,000 steps per 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 5,000 steps per 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 three to four 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 2013, the NHLBI updated its evidence-based algorithm to help guide clinicians in identifying and treating obesity [75]. Other guidelines are also available. The ADA offers strategies for weight management through lifestyle modification for both prevention and treatment of type 2 diabetes [109]. The Institute for Clinical Systems Improvement, a nonprofit collaboration of healthcare providers and organizations, last updated their guideline on obesity management and prevention in 2013 [110].

Pharmacotherapy

According to NHLBI guidelines, obese patients with a BMI ≥30, or overweight patients with a BMI ≥27 and concomitant obesity-related risk factors or diseases, such as hypertension, diabetes, or dyslipidemia, are candidates for drug therapy [75]. Although a useful tool, it is important to remember that drug therapy is only one part of the treatment. 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 [75]. In addition, patients should have realistic expectations of drug therapy and not have contraindications to the drugs.

Orlistat is approved by the U.S. Food and Drug Administration (FDA) for long-term treatment of obesity; phentermine/topiramate is approved for short-term treatment only [75]. Average weight loss with orlistat is modest, typically 2–4 kg [111]. Orlistat is also associated with weight loss of around 3% more than diet alone in individuals who are overweight or obese [112].

Orlistat is a gastric and pancreatic lipase inhibitor. It reduces the absorption of 30% of a patient's dietary fat intake [113]. Orlistat 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 [114]. These data are statistically significant. Like most medications, orlistat does have side effects, including fecal urgency, oily spotting, and flatulence [113; 115]. The drug may not be suitable for patients with bowel conditions, such as ulcerative colitis and Crohn disease, or irritable bowel syndrome. Typical dosage is 120 mg with each meal [113; 115].

In 2012, the FDA approved the first new weight-loss medications in more than a decade: lorcaserin and phentermine/topiramate [113]. However, lorcaserin was voluntarily withdrawn from the market by the manufacturer in 2020 due to results from safety clinical trials showing an increased occurrence of cancer [116; 117].

Phentermine/topiramate (extended-release) combines an anorexiant and an anticonvulsant to improve short-term weight-loss outcomes in patients who have already attempted lifestyle changes (i.e., calorie-restricted diet and increased physical activity) [113]. Eligible patients will have a BMI ≥30 or a BMI ≥27 with a weight-related comorbidity [118]. The recommended initial dose of phentermine/topiramate is 3.75 mg phentermine/23 mg topiramate extended-release once per day for 14 days [113; 118]. The dose may be titrated to a maximum of 15 mg/92 mg [113]. The medication is contraindicated in persons with glaucoma and hyperthyroidism and is not recommended for patients with a recent history of stroke or heart disease [113; 118]. It is also teratogenic, with proven fetal defects with first trimester exposure. Therefore, all women of childbearing age should use effective contraception consistently while taking the drug and have documented proof of a negative pregnancy test prior to the initiation of treatment and every month thereafter [113; 118].

In 2014, combination bupropion/naltrexone was approved as a treatment option for chronic weight management [119]. Studies show that these drugs are effective in improving the percentage of total body weight lost compared to placebo. The dosage is gradually titrated up, starting with one tablet (naltrexone 8 mg/bupropion 90 mg) once daily in the morning for one week and increasing one daily tablet each week for four weeks. The maintenance dose is two tablets twice daily [113]. If 5% of initial body weight has not been lost after 12 weeks, the medication should be discontinued.

Any patient taking bupropion should be carefully monitored for suicidal ideation and behaviors [113; 119]. This medication may also increase blood pressure and heart rate and is contraindicated in patients with hypertension. It is also contraindicated in patients with a history of seizures, who are taking another bupropion-containing medication, or who are pregnant.

Also in 2014, the GLP-1 receptor agonist liraglutide was approved by the FDA for chronic weight management. Traditionally used to treat diabetes, liraglutide has been found to aid in appetite suppression and weight loss [120]. The dosage of liraglutide used for weight management (3 mg) differs from the dose used in diabetes medication regimens (1.8 mg), and the safety and efficacy of this higher dose for the treatment of diabetes has not been established [120]. This medication is contraindicated in those with a personal or family history of thyroid cancer.

In 2021, the FDA approved semaglutide injection for chronic weight management in adults with obesity (BMI ≥30) or overweight (BMI ≥27) with at least one weight-related condition (e.g., hypertension, type 2 diabetes, hyperlipidemia) [121]. This agent is a glucagon-like peptide-1 (GLP-1) receptor agonist and is intended to be used in conjunction with lifestyle changes. When used for weight management, semaglutide is administered subdermally at a dose of 2.4 mg once weekly [121].

In 2020, the FDA approved setmelanotide for chronic weight management in patients six years of age and older with a genetic obesity disorder, such as deficiency of pro-opiomelanocortin (POMC) [113]. Setmelanotide facilitates weight loss in patients with the indicated genetic obesity disorders by restoring appetite control and thereby reducing food intake and weight. The agent does not treat the hereditary defects that cause obesity [122]. Setmelanotide can bind to and activate multiple melanocortin receptors involved in key physiological functions of the body (e.g., feeding behavior, energy balance, cardiovascular function, immune response). The effectiveness of the agent was assessed in phase 3 clinical trials in which 80% of the patients with POMC deficiency lost at least 10% of their body weight [123].

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 [75]. Other selection criteria include a good social support system, no active substance abuse, no clinically significant or unstable psychopathology, and previously demonstrated adherence to medical recommendations [75; 124].

Data from the Behavioral Risk Factor Surveillance System indicate that between 2000 and 2010, the prevalence of a BMI greater than 40 (calculated from self-reported height and weight) increased by 70% in the United States [125]. Data from the National Center for Health Statistics for 2017 to 2018 showed a BMI of 40 or greater for 9.2% of adults [126]. A 2012 survey of more than 350,000 Americans conducted by Gallup found that 3.6% of American adults self-reported a BMI greater than 40 [127]. These figures are likely underestimates, as measured weight tends to be higher than self-reported numbers.

There is fair to good evidence that surgical intervention, such as gastric bypass, vertical banded gastroplasty, and adjustable banding, can produce substantial weight loss (i.e., 28 kg to more than 40 kg). Surgery may also lead to improvements in quality of life and obesity-related diseases such as hypertension and diabetes [124]. Surgical procedures result in weight loss either by restricting the size of the stomach or 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. A meta-analysis of 136 studies of bariatric surgery (conducted between 1990 and 2003) involved a total of 22,094 weight loss patients [128]. 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). The objective of the analysis was to determine the impact of bariatric surgery on weight loss, operative mortality (at 30 days), and four 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 [128].

Patients lost an average 61% of their excess 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 [128]. 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 nonsurgical treatment for weight loss and control of certain comorbid conditions in people with a BMI of 40 or greater. For people with lower BMIs, the researchers felt that more data was needed, although surgery appeared to be superior for those with a BMI of 30 to 39 [129]. The results of two systematic reviews published in 2013 found that, compared with non-surgical treatment of obesity, bariatric surgery leads to greater weight loss and higher remission rates of type 2 diabetes and metabolic syndrome in both morbidly obese and nonmorbidly obese adults [130; 131]. 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 [114]. This conclusion is supported by the updated AHA/ACC/TOS guidelines [75]. In 2019, the American Association of Clinical Endocrinologists, the Obesity Society, the American Society for Metabolic and Bariatric Surgery (ASMBS), the Obesity Medicine Association, and the American Society of Anesthesiologists released updated guidelines for the perioperative care of the patient undergoing bariatric surgery [132; 133; 134; 135]. Their selection criteria include BMI greater than 40 if no comorbidities are present, greater than 35 if there is one or more obesity-associated comorbidity, or greater than 30 with diabetes or metabolic syndrome [132; 134; 135]. In 2022, the ASMBS and the International Federation for the Surgery of Obesity and Metabolic Disorders released updated indications for metabolic and bariatric surgery to include individuals with a BMI of 35 or more, regardless of presence, absence, or severity of comorbidities. They indicated also that metabolic and bariatric surgery be considered for individuals with metabolic disease and BMI of 30–34.9 [136].

The Swedish Obese Subjects (SOS) study showed that gastric bypass led to a 20 kg weight loss after eight years and reduced progression to type 2 diabetes by 81% compared with usual care [137]. The SOS study was a prospective, nonrandomized, intervention trial involving 4,047 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. The unadjusted overall mortality was reduced by 23.7% in the surgery group (relative to the control group); the gender-, age-, and risk factor-adjusted mortality reduction was 30.7% [138].

Metabolic syndrome has been shown to improve or resolve following weight-loss surgery [130; 131; 139; 140; 141; 142]. 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 [139]. 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 [143]. The risk of cardiovascular events appears to be increased in people with IFG and IGT [144]. IGT may have a larger effect, although more research is needed to evaluate this [143; 144; 145; 146].

In addition, the risk of diabetes increases in relation to BMI. According to data from the National Health and Nutrition Examination Survey from 2005 to 2016, among adults 18 years of age and older diagnosed with diabetes, 89.0% were overweight (BMI ≥25), 27.6% had a BMI 25.0–29.9, 45.8% were obese (BMI 30.0–39.9), and 15.5% were extremely obese (BMI ≥40) [20]. 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 [147; 148; 149]. One study found that the prevalence of diabetes rose by 2.59% per year during the period 1988–2014. Increased adiposity was attributed to 72% of the rise in diabetes prevalence, with results consistent for men and women [150]. As stated, the AMA adopted a new policy that recognizes the issues with BMI measurement and suggest that it be used in conjunction with other valid measures of risk (e.g., visceral fat, body adiposity index, waist circumference, race, ethnicity) [31].

Patients with diabetes are two to four times more likely to die from cardiovascular disease than patients without diabetes [151]. 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 3,234 patients with IFG or IGT to placebo, metformin, or intensive lifestyle (i.e., intensive nutritional and exercise counseling) changes [152]. The intensive lifestyle therapy reduced progression to type 2 diabetes nearly 60% over an average of three years. When overweight patients lost 7% to 10% of their body weight and took 30-minute walks five days per 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 [153]. Of note, metformin has not been shown to reduce the risk of cardiovascular disease in patients with metabolic syndrome, prediabetes, or diabetes, although it has reduced the incidence of diabetes-related endpoints, such as stroke [152]. Metformin has been associated with weight loss, but may lead to adverse gastrointestinal effects (e.g., dyspepsia, diarrhea) and can be associated with the development of vitamin B12 deficiency over time [154]. Metformin therapy is often contraindicated in older adults due to renal insufficiency or risk of significant heart failure [153].

More than 3,000 patients who were part of the DPP were studied to determine whether diet and exercise or metformin prevents or reverses metabolic syndrome in patients with IGT [155]. 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, the 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 the 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 [153; 155].

In the Finnish Diabetes Prevention Study (DPS), 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 [156]. 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 [157]. The active intervention period lasted an average of four years, and patients were followed for a median of seven 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. After the four-year active intervention period, participants still free of diabetes and willing to continue their participation (200 in the intervention group, 166 in the control group) were further followed until diabetes diagnosis, dropout, or the end of 2009 (median total follow-up: nine years) [158]. The original intervention group participants sustained lower body weight, lower fasting and two-hour blood glucose, and a healthier diet. Adherence to lifestyle changes during the intervention period predicted greater risk reduction and long-term prevention of progression to type 2 diabetes [158]. A 2008 Chinese study offers 20 years of follow-up for a lifestyle intervention in patients with IGT [159]. Patients in this study were randomly assigned to diet, exercise, diet plus exercise, or a control group. Active intervention was offered for the first six 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 three 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 [160]. In the Troglitazone in Prevention of Diabetes (TRIPOD) study, troglitazone reduced progression from gestational diabetes to type 2 diabetes by 55% [161]. 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 [162; 163]. 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 [164; 165]. It should be noted that in February 2011 the FDA issued a public safety announcement regarding the cardiovascular risks (including heart attack) associated with the use of rosiglitazone in certain patients. The safety information was added to physician labeling and patient medication guides for the drug [166]. In 2011, the FDA further restricted the prescribing and use of rosiglitazone-containing medicines, but these restrictions were removed in 2013 [167]. In 2015, the FDA eliminated the Risk Evaluation and Mitigation Strategy (REMS) for rosiglitazone-containing diabetes medications. The REMS were determined to no longer be necessary to ensure that the benefits of rosiglitazone medications outweigh the risks [167].

In June 2011, the FDA issued a safety announcement regarding the increased risk of bladder cancer in patients using pioglitazone for more than one year [168]. In 2016, the FDA issued an additional safety announcement about pioglitazone in which the agency concluded that use of pioglitazone may be linked to an increased risk of bladder cancer. The FDA approved label updates to describe the additional studies reviewed that led to this conclusion [169]. In the Study to Prevent Non-Insulin Dependent Diabetes Mellitus (STOP-NIDDM), 1,429 patients with IGT were randomized to receive either acarbose or placebo [170; 171]. 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 [172]. 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 IGF and IGT plus other risk factors [153; 173]. Additionally, a 10-year cost-effectiveness analysis, a follow-up to the DPP, found that treatment with metformin or a lifestyle intervention reduced the costs of medical care by $1,700 and $2,600 per person, respectively, compared to placebo during the 10-year period [174].

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 recommendation for testing requires a 9- to 12-hour fast prior to laboratory measurements [175; 176]. 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.

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 of the NHLBI discontinuing its publication of clinical guidelines, the ATP IV panel joined with the ACC and AHA, and a new guideline for treatment of blood cholesterol to reduce cardiovascular risk was published in 2014 and updated in 2018 [177; 178]. Although the 2014 guideline did not mention the role of metabolic syndrome or insulin resistance on the treatment of dyslipidemia, it is addressed in the 2018 update [178].

When addressing dyslipidemia in the absence of other cardiovascular risk factors, physicians should first target LDL levels that are greater than 190 mg/dL [177; 178]. 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 [178]. Ideally, HDL for men should be at least 40 mg/dL and at least 50 mg/dL for women [179; 180]. When addressing dyslipidemia in the presence of chronic coronary disease, high-intensity statin therapy is recommended with the aim of achieving a 50% or greater reduction in LDL levels. In patients in whom high-intensity stain therapy is contraindicated or not tolerated, moderate-intensity statin therapy is recommended with the aim of achieving a 30% to 49% reduction in LDL levels. Adherence to changes in lifestyle and effects of lipid-lowering medication should be assessed by measurement of fasting lipids in 4 to 12 weeks after stain initiation [181]. Annual follow-up to assess for symptoms, change in functional status, adequacy of lifestyle and medical interventions, and monitoring for complications also is recommended [181].

Treatment begins with lifestyle changes (i.e., 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 [182]. Several studies have demonstrated the benefit of lifestyle changes in managing dyslipidemia. For instance, researchers in one study randomized 197 men and 180 postmenopausal women with high LDL and low HDL to aerobic exercise, diet, diet and exercise, or no treatment [183]. 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 [184; 185; 186].

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 using combination therapy [185]. Combination therapy typically involves a statin and a triglyceride-lowering drug, such as a fibrate (e.g., gemfibrozil, fenofibrate) or niacin. The fibrates typically lower triglyceride levels by 20% to 50% and raise HDL cholesterol by 10% to 35% [185]. Additionally, fibrates used either alone or in combination with statins have been associated with reduced risk of cardiovascular events in patients with dyslipidemia [187; 188; 189]. In 2016, the FDA withdrew its approval of the indications related to the co-administration of fibrates with a statin as the agency concluded that the benefit of adding a fibrate to a statin does not outweigh the risk for most patients [190]. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial found that the combination of a fibrate with a statin is associated with lower mortality in diabetic patients with triglycerides >204 mg/dL and an HDL level <34 mg/dL [151; 191]. For this reason, use of the combination in this subgroup population is recommended by the Institute for Clinical Systems Improvement [182]. Guidelines from the AHA/ACC and others note that more than one-half of the ACCORD trial participants had established cardiovascular disease at baseline, and that no benefit was observed in this subgroup of patients to justify the addition of fenofibrate to background statin therapy. These guidelines recommend that fenofibrate only be considered in patients with triglycerides ≥500 mg/dL to reduce the risk of acute pancreatitis [192]. 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, and requires monitoring of glucose in long-term treatment [193]. 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 one year [194].

Niacin increased glucose levels by 8.1 mg/dL in the patients with diabetes, compared with an increase of 6.3 mg/dL in the subjects without diabetes. The Assessment of Diabetes Control and the Evaluation of the Efficacy of Niaspan Trial (ADVENT) randomized 148 patients with type 2 diabetes to placebo or extended-release niacin [195]. 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 Treatment Study (HATS) investigated the effects of combined therapy with simvastatin and niacin in patients with coronary artery disease and low HDL levels [196]. 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 eight months, the glucose levels returned to pretreatment levels and remained stable for the remainder of the study. The Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health (AIM-HIGH) trial found that, among patients with cardiovascular disease and LDL levels less than 70 mg/dL, there was no benefit from the addition of niacin to statin therapy during a 36-month follow-up period, despite significant improvements in HDL cholesterol and triglyceride levels [197]. Another niacin trial in secondary prevention, the Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) trial also found that the addition of extended-release niacin-laropiprant to statin-based LDL-lowering therapy did not significantly reduce the risk of major vascular events but did increase the risk of serious adverse events. (Note: Laropiprant, a prostaglandin receptor antagonist, is no longer available [198].) The ADA generally does not recommend the use of niacin as it may increase the risk of stroke [153].

HYPERTENSION

Hypertension remains a significant cause of morbidity and mortality. In the United States, 29% of adults have hypertension, with a similar prevalence for men (30.2%) and women (27.7%). Among adults with hypertension, approximately 48% have their hypertension under control [199]. 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 myocardial 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 [200].

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 cardiovascular disease (***Table 2***) [201]. Prehypertension includes people with a systolic blood pressure of 120–139 mm Hg or a diastolic blood pressure of 80–89 mm Hg. Though a report from the JNC 8 panel was released in 2014, it does not include information related to the categorization of blood pressure levels [202]. Keep in mind that ATP III includes a blood pressure of 130/85 mm Hg or greater as a risk factor for metabolic syndrome. The JNC 8 Committee recommends antihypertensive drugs in patients, including those with diabetes, with blood pressures greater than 140/90 mm Hg. The threshold levels are slightly higher (i.e., ≥150/90 mm Hg) for adults 60 years of age or older [202].

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: [201] *Table 2*

As noted, the report of members of the JNC 8 was published in 2014, but this new guideline is limited to the pharmacologic management of hypertension; much of the guidance addressing screening, diagnosis, and lifestyle modification has been removed [202]. As such, the guidance originally provided in the JNC 7 related to counseling and lifestyle changes remains current.

Patients with either prehypertension or stage 1 hypertension should initially be treated with lifestyle modifications, including weight reduction, dietary modifications (i.e., adopting the Dietary Approach to Stop Hypertension [DASH] eating plan), dietary sodium reduction, physical activity, and moderation of alcohol consumption [201]. Exercise has been demonstrated to reduce hyperinsulinemic responses to glucose challenges in patients with metabolic syndrome [203]. Researchers evaluated the effects of a six-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 [203]. These results suggest that exercise is an effective treatment for hyperinsulinemia and lowering of diastolic blood pressure in patients with metabolic syndrome.

For patients with hypertension and overweight/obesity, the Department of Veterans Affairs and the Department of Defense suggest offering a diet directed at weight loss for the treatment of hypertension.

(https://www.healthquality.va.gov/guidelines/CD/htn. Last accessed October 10, 2023.)

Strength of Recommendation: Weak for

In 2002, a meta-analysis of 54 controlled trials examined the effects of aerobic exercise on systolic and diastolic blood pressure [204]. 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 and normotensive participants and in overweight 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 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) [205].

Along with exercise and the previous advice given about nutrition, healthcare providers may wish to consider the 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. The first DASH study involved 459 adults; approximately 27% of the participants had high blood pressure. The study compared three eating plans: the first was similar to what Americans regularly eat; the second was similar to what Americans regularly eat plus more fruits/vegetables; and the third was the DASH eating plan. All three plans included about 3,000 mg of sodium per day. Participants who followed both the second and DASH plans had reduced blood pressure, but the DASH plan produced the greatest effect. The second DASH study involved 412 participants and examined the effect on blood pressure of a reduced dietary sodium intake. Participants were randomly assigned to one of two plans—either a typical American diet or the DASH eating plan—and to one of three sodium levels: 3,300 mg/day, 2,300 mg/day, or 1,500 mg/day. Results showed that reduced dietary sodium produced lowered blood pressure for both eating plans, with the greatest blood pressure reductions for the DASH plan at 1,500 mg of sodium daily [181; 206]. Numerous studies have shown the DASH diet to lower blood pressure [207; 208; 209]. The DASH-Sodium trial showed that reduced sodium may improve biomarkers of cardiac injury, inflammation, and cardiac strain [210]. In addition, increasing the intake of fiber in the typical Western diet and combining exercise and weight loss with the DASH diet may contribute to the prevention of hypertension [211; 212]. The JNC 7 additionally recommended a public health strategy to complement the treatment of hypertension, particularly among individuals with prehypertension. A population approach that decreases the blood pressure level in the general population by even modest amounts has the potential to substantially reduce morbidity and mortality or at least delay the onset of hypertension [201].

If blood pressure remains high, pharmacotherapy should be considered. More than two-thirds of individuals with hypertension cannot be controlled on one drug and will require two or more antihypertensive agents selected from different drug classes [201]. 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 [213; 214; 215]. ARBs may have similar effects. The Losartan Intervention for Endpoint (LIFE) trial demonstrated lower rates of nonfatal and fatal cardiovascular disease in patients with diabetes, hypertension, and left ventricular hypertrophy who took the ARB losartan compared to those that took atenolol, a beta-blocker [216]. Losartan was also more effective than atenolol in reducing all-cause mortality. However, authors of a 2017 Cochrane Review concluded that initiating treatment of hypertension with ARBs leads to modest reductions in cardiovascular risk and little or no effects on mortality. They also found that ARB effects are inferior to those of other antihypertensive drugs [217].

For most cases of hypertension in the general non-Black population, the JNC 8 recommends the use of a thiazide-type diuretic, calcium channel blocker, ACE inhibitor, or ARB as initial antihypertensive therapy due to their propensity to prevent cardiovascular complications associated with hypertension [202]. Results of a 2014 Cochrane Review indicate that thiazides also are more effective at lowering systolic blood pressure than ACE inhibitors, ARBs, and renin inhibitors [218]. In the Black population, the preferred first-line agents are thiazide diuretics or calcium channel blockers. Healthcare professionals treating patients with metabolic syndrome should be aware that thiazides have been associated with insulin resistance and other metabolic changes [113]. However, at lower doses, changes in glucose levels appear to be small [219].

As noted, 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 six to eight 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 cardiovascular 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 may be considered to help control the risk factors.

RESOURCES

American College of Cardiology
https://www.acc.org

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

National Institutes of Health
Medline Plus: Metabolic Syndrome
https://medlineplus.gov/metabolicsyndrome.html

American Heart Association
https://www.heart.org

Heart Rhythm Society
https://www.hrsonline.org

U.S. Department of Agriculture
MyPlate.gov
https://www.myplate.gov

U.S. Food and Drug Administration:
How to Understand and Use the Nutrition Facts Label
https://www.fda.gov/food/new-nutrition-facts-label/how-understand-and-use-nutrition-facts-label

Implicit Bias in Health Care

The role of implicit biases on healthcare outcomes has become a concern, as there is some evidence that implicit biases contribute to health disparities, professionals' attitudes toward and interactions with patients, quality of care, diagnoses, and treatment decisions. This may produce differences in help-seeking, diagnoses, and ultimately treatments and interventions. Implicit biases may also unwittingly produce professional behaviors, attitudes, and interactions that reduce patients' trust and comfort with their provider, leading to earlier termination of visits and/or reduced adherence and follow-up. Disadvantaged groups are marginalized in the healthcare system and vulnerable on multiple levels; health professionals' implicit biases can further exacerbate these existing disadvantages.

Interventions or strategies designed to reduce implicit bias may be categorized as change-based or control-based. Change-based interventions focus on reducing or changing cognitive associations underlying implicit biases. These interventions might include challenging stereotypes. Conversely, control-based interventions involve reducing the effects of the implicit bias on the individual's behaviors. These strategies include increasing awareness of biased thoughts and responses. The two types of interventions are not mutually exclusive and may be used synergistically.

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