The Metabolic Syndrome
Practical Guide to Origins and Treatment: Part I
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The metabolic syndrome (MetS), a cluster of metabolic abnormalities with insulin resistance as a major characteristic, has gone by several names over the past two decades. The diagnostic criteria proposed by the Adult Treatment Program III (ATP III) of the National Cholesterol Education Program (NCEP) have led to greater awareness of the components and treatment strategies. Five diagnostic traits are listed in the ATP III version of the MetS (Table; referred to as the “metabolic syndrome”), and the presence of any 3 of these factors is considered sufficient for diagnosis. This practical review will consider each in turn, providing advice for cardiologists, internists, and other health care providers who are diagnosing and treating persons with the syndrome in an effort to prevent a variety of clinical outcomes.

The major adverse consequence of the MetS is cardiovascular disease (CVD). Several of the metabolic abnormalities associated with the syndrome, in fact, are CVD risk factors. One of these abnormalities, insulin resistance, also predisposes to the development of type 2 diabetes mellitus (T2DM).

In age-adjusted estimates from the National Health and Nutrition Examination Survey III in 1998 to 1994, approximately 24% of adult Americans had ≥3 of the 5 MetS criteria. Key determinants of greater prevalence were age and ethnicity. Prevalence rates were highest in Mexican Americans and were successively lower in white, African American and other racial groups. These published estimates included persons with diabetes mellitus who had met the 1998 fasting glucose criteria (≥126 mg/dL [8.0 mmol/L]) of the American Diabetes Association. This article will focus on the features of the MetS in persons without diabetes mellitus, although most persons with T2DM also have the MetS. Moreover, the therapeutic approaches to metabolic risk factors described here also can be applied to most patients with T2DM.

Cardiovascular Risk Assessment in Patients With MetS
The intensity of management of risk factors in the MetS depends in part on assessment of the patient’s global risk for CVD, particularly coronary heart disease (CHD). Patients at higher risk deserve more aggressive risk-reduction therapy. According to ATP III guidelines, risk assessment is best carried out using Framingham risk scoring. Some clinicians have the mistaken impression that the presence of the MetS indicates that a patient has a high-risk status, similar to patients with established CHD or T2DM. Such is not the case. Absolute risk in patients with MetS is variable, and some patients are at only moderate or moderately high risk for CHD.

Some of the risk factors listed for the MetS are not included in Framingham risk scoring. These include abdominal obesity, a proinflammatory state (high levels of C-reactive protein), impaired fasting glucose or impaired glucose tolerance, and a prothrombotic state (high levels of fibrinogen). ATP III guidelines do not recommend routine measurement of these emerging risk factors, but they are listed as optional measures. If they are found to be abnormal in patients with characteristics of the MetS, the physician has the option to adjust risk higher than estimated from Framingham risk scoring. This approach, however, is somewhat problematic because reliable, quantitative adjustments to risk have not been developed.

Abdominal Adiposity
What Is the Background?
Several decades ago it was recognized by European investigators that abdom-
inal adiposity was related to greater risk of cardiovascular events. The first investigations focused on the ratio of waist/hip girth as the critical measurement. More recent studies have shown that greater waist circumference alone is related to an increase in cardiovascular events, greater fasting insulin levels, increased insulin resistance in metabolic ward studies, and increased abdominal fat assessed by modern techniques such as computerized tomographic scanning.

Traditional measures of determining adiposity, such as relative weight tables circulated by insurance providers, are important determinants of a variety of cardiovascular risk factors, especially hypertension, diabetes mellitus, and dyslipidemia. Body mass index (BMI), the weight in kilograms divided by the height in meters squared, has become the measure commonly used to assess total adiposity and is thought to play a secondary role behind abdominal adiposity in the development of several metabolic risk processes. Investigators who have studied the effects of total obesity (BMI) and abdominal obesity (waist or waist/hip measurements) on outcomes, have typically found that both measures of obesity increase risk of heart disease and diabetes mellitus.

How Do You Make the Diagnosis?
Three simple measurements should be made on all patients, as follows: height, weight, and maximal abdominal girth using a tape measure. The body mass should be calculated or read off a chart, and the physician should inform the patient of his or her category: normal (BMI 18.5 to 25 kg/m²), overweight (BMI 25 to 30 kg/m²), or obese (BMI >30 kg/m²). An increased waist girth (≥ 35 in [88 cm] for women, ≥ 40 in [103 cm] for men) defines excess abdominal adiposity according to the ATP III criteria. Slightly different criteria are being considered in other populations, especially among Asians. The appropriate time to do this is at the time of an initial visit.

What Are the Treatment Options for Excess Adiposity in the MetS?
A weight-reduction diet should be prescribed for obese patients. Various strategies are available, but the most common approach for overweight persons who may have the MetS is a balanced-calorie diet. If this diet prescription is followed, the patient would be expected to gradually approach a normal weight category. A typical prescription would be to estimate the patient’s current needs with a dietary and physical activity history. A reduction in calories by approximately 500 cal/d is often an acceptable strategy to achieve the goal of an ideal weight. Take the example of a sedentary woman, 50 years of age, height 66 inches, weight 190 pounds, BMI 29 kg/m², and no reported exercise. By the Harris-Benedict equation, the usual caloric intake would be estimated at 1556 cal/d. Dietary consumption of 1050 cal/d, a 500 cal/d lower intake, with no change in exercise would be expected to lead to a weight loss of approximately one pound a week. The ideal weight target for this woman would be 129 pounds. A panel of obesity experts has recommended an initial goal of weight loss as approximately 10% of baseline and a reasonable time to achieve this goal as 6 months. As discussed in more detail below, this diet should also follow guidelines for cholesterol (<300 g/d) and fat intake (25% to 35% calories as fat) as set forward in the NCEP ATP III guidelines.

More aggressive approaches are possible for obese individuals and in special situations. Such care is typically provided in a weight loss clinic. Very restrictive diets for weight management include other treatment options, usually overseen by an obesity specialist. One of the options is a very low-calorie liquid diet of 500 to 1200 calories/d and requiring intensive outpatient medical supervision and laboratory monitoring of electrolyte levels and liver function. Unfortunately, long-term maintenance of lost weight has been problematic. Weight is usually regained, and behavioral modification and physical activity components are underprescribed by healthcare providers.

Pharmacological agents are available to treat persons with excess adiposity. The 2 main classes of agents are appetite suppressants and inhibitors of nutrient absorption. In the appetite suppressant group, common choices include phentermine derivatives (noradrenergic) and sibutramine (inhibitor of serotonin reuptake and norepinephrine). These agents are usually taken in the late morning, lead to decreased appetite in the late afternoon and evening, and may have side effects related to noradrenergic excess. In the nutrient inhibitor class, orlistat (an inhibitor of gastrointestinal lipase) is the only medication currently available. It prevents the absorption of approximately 30% of the fat that is consumed and must be taken at the time of the fat consumption. Undesirable side effects such as flatulence and oil leakage in the stool often occur early in the course of treatment with this medication. Each of these weight loss medications is typically used as a single agent. The expected weight loss varies greatly but is typically 5% to 10% of initial weight. In randomized clinical trials, orlistat in obese persons with T2DM at baseline led to improved glycemic control and a weight re-
duction of 6% over 1 year versus 4% weight loss with placebo. A recently published meta-analysis concerning the efficacy of pharmacological agents for obesity reported that average weight loss was approximately 4 kilograms more than for placebo users and that no drug or class of drugs was clearly superior. Many persons who do not respond to weight loss diet or medications are candidates for weight loss surgery if they are extremely obese (BMI >40 kg/m²) or if they have a BMI >35 to 40 kg/m² and one or more comorbid conditions, items that are typical elements of the MetS.

A successful surgical program to treat obesity includes psychological profiling and extensive preoperative screening for conditions such as prior coronary artery disease. One of the most popular and effective procedures is a vertically banded gastric bypass surgery, and weight typically declines 40% at 1 year and 62% at 5 years. Several components of the MetS usually improve in concert with weight loss after surgery, including lipids and glucose levels, but assiduous follow-up is needed. Monitoring of vitamin and hematologic status, adherence to specific postoperative dietary instructions, and psychological issues are important for long-term success after weight loss surgery. Laparoscopic techniques that include putting a collar around the proximal end of the stomach are now available. The non-invasive methods have been associated with less weight loss, and their long-term utility has still not been fully evaluated.

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References