metabolic syndrome. In general, recommendations for weight loss include a combination of caloric restriction, increased physical activity, and behavior modification. Caloric restriction is the most important component, whereas increases in physical activity are important for maintenance of weight loss. Some but not all evidence suggests that the addition of exercise to caloric restriction may promote greater weight loss from the visceral depot. The tendency for weight regain after successful weight reduction underscores the need for long-lasting behavioral changes.

Diet Before prescribing a weight-loss diet, it is important to emphasize that it has taken the patient a long time to develop an expanded fat mass; thus, the correction need not occur quickly. Given that ~3500 kcal = 1 lb of fat, ~500-kcal restriction daily equates to weight reduction of 1 lb per week. Diets restricted in carbohydrate typically provide a rapid initial weight loss. However, after 1 year, the amount of weight reduction is minimally reduced or no different from that with caloric restriction alone. Thus, adherence to the diet is more important than which diet is chosen. Moreover, there is concern about low-carbohydrate diets enriched in saturated fat, particularly for patients at risk for CVD. Therefore, a high-quality dietary pattern—i.e., a diet enriched in fruits, vegetables, whole grains, lean poultry, and fish—should be encouraged to maximize overall health benefit.

Physical Activity Before a physical activity recommendation is provided to patients with the metabolic syndrome, it is important to ensure that the increased activity does not incur risk. Some high-risk patients should undergo formal cardiovascular evaluation before initiating an exercise program. For an inactive participant, gradual increases in physical activity should be encouraged to enhance adherence and avoid injury. Although increases in physical activity can lead to modest weight reduction, 60–90 min of daily activity is required to achieve this goal. Even if an overweight or obese adult is unable to undertake this level of activity, a significant health benefit will follow from at least 30 min of moderate-intensity activity daily. The caloric value of 30 min of a variety of activities can be found at *www.heart.org/HEARTORG/GettingHealthy/WeightManagement/LosingWeight/Losing-Weight_UCM_307904_Article.jsp*. Of note, a variety of routine activities, such as gardening, walking, and housecleaning, require moderate caloric expenditure. Thus, physical activity need not be defined solely in terms of formal exercise such as jogging, swimming, or tennis.

Behavior Modification Behavioral treatment typically includes recommendations for dietary restriction and more physical activity, resulting in weight loss that benefits metabolic health. The subsequent challenge is the duration of the program because weight regain so often follows successful weight reduction. Long-term outcomes may be enhanced by a variety of methods, such as the Internet, social media, and telephone follow-up to maintain contact between providers and patients.

Obesity (See also Chap. 416) In some patients with the metabolic syndrome, treatment options need to extend beyond lifestyle intervention. Weight-loss drugs come in two major classes: appetite suppressants and absorption inhibitors. Appetite suppressants approved by the U.S. Food and Drug Administration include phentermine (for short-term use [3 months] only) as well as the more recent additions phentermine/topiramate and lorcaserin, which are approved without restrictions on the duration of therapy. In clinical trials, the phentermine/topiramate combination has resulted in ~10% weight loss in 50% of patients. Side effects include palpitations, headache, paresthesias, constipation, and insomnia. Lorcaserin results in less weight loss—typically ~5% beyond placebo—but can cause headache and nasopharyngitis. Orlistat inhibits fat absorption by ~30% and is moderately effective compared with placebo (~5% more weight loss). Orlistat has been shown to reduce the incidence of type 2 diabetes, an effect that was especially evident among patients with impaired glucose tolerance at baseline. This drug is often difficult of take because of oily leakage per rectum.

Metabolic or bariatric surgery is an option for patients with the metabolic syndrome who have a body mass index >40 kg/m^2, or >35 kg/m^2 with comorbidities. An evolving application for metabolic surgery includes patients with a body mass index as low as 30 kg/m^2 and type 2 diabetes. Gastric bypass or vertical sleeve gastrectomy results in dramatic weight reduction and improvement in the features of the metabolic syndrome. A survival benefit with gastric bypass has also been realized.

LDL CHOLESTEROL (SEE ALSO CHAP. 421)

The rationale for the NCEP:ATPIII's development of criteria for the metabolic syndrome was to go beyond LDL cholesterol in identifying and reducing the risk of CVD. The working assumption by the panel was that LDL cholesterol goals had already been achieved and that increasing evidence supports a linear reduction in CVD events as a result of progressive lowering of LDL cholesterol with statins. For patients with the metabolic syndrome and diabetes, a statin should be prescribed. For those patients with diabetes and known CVD, the current evidence supports a maximum of penultimate dose of a potent statin (e.g., atorvastatin or rosuvastatin). For those patients with the metabolic syndrome but without diabetes, a score that predicts a 10-year CVD risk exceeding 7.5% should also take a statin. With a 10-year risk of <7.5%, use of statin therapy is not evidence based.

Diets restricted in saturated fats (<7% of calories) and *trans*-fats (as few as possible) should be applied aggressively. Although less evidence exists, dietary cholesterol should also be restricted. If LDL cholesterol remains elevated, pharmacologic intervention is needed. Treatment with statins, which lower LDL cholesterol by 15–60%, is evidence based and is the first-choice medication intervention. Of note, for each doubling of the statin dose, LDL cholesterol is further lowered by only ~6%. Hepatotoxicity (more than a threefold increase in hepatic aminotransferases) is rare, and myopathy is seen in ~10% of patients. The cholesterol absorption inhibitor ezetimibe is well tolerated and should be the second-choice medication intervention. Ezetimibe typically reduces LDL cholesterol by 15–20%. The bile acid sequestrants cholestyramine, colestipol, and colesevalam may be more effective than ezetimibe but, because they can increase triglyceride levels, must be used with caution in patients with the metabolic syndrome. In general, bile sequestrants should not be administered when fasting triglyceride levels are >250 mg/dL. Side effects include gastrointestinal symptoms (palatability, bloating, belching, constipation, anal irritation). Nicotinic acid has modest LDL cholesterol–lowering capabilities (<20%). Fibrates are best employed to lower LDL cholesterol when both LDL cholesterol and triglycerides are elevated. Fenofibrate may be more effective than gemfibrozil in this setting.

TRIGLYCERIDES (SEE ALSO CHAP. 421)

The NCEP:ATPIII has focused on non-HDL cholesterol rather than on triglycerides. However, a fasting triglyceride value of <150 mg/dL is recommended. In general, the response of fasting triglycerides relates to the amount of weight reduction achieved: a weight reduction of >10% is necessary to lower fasting triglyceride levels.

A fibrate (gemfibrozil or fenofibrate) is the drug of choice to lower fasting triglyceride levels, which are typically reduced by 30–45%. Concomitant administration with drugs metabolized by the 3A4 cytochrome P450 system (including some statins) increases the risk of myopathy. In these cases, fenofibrate may be preferable to gemfibrozil. In the Veterans Affairs HDL Intervention Trial, gemfibrozil was administered to men with known CHD and levels of HDL cholesterol <40 mg/dL. A coronary disease event and mortality rate benefit was experienced predominantly among men with hyperinsulinemia and/or diabetes, many of whom were identified retrospectively as having the metabolic syndrome. Of note, the degree of triglyceride lowering in this trial did not predict benefit. Although levels of LDL cholesterol did not change, a decrease in LDL particle number correlated with benefit. Several additional clinical trials have not shown