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of choice in children and in women who are pregnant, lactating, or actively trying to conceive. However, they are otherwise fourth- or fifth-line drugs for LDL-C reduction in other settings.

Specialized Drugs for HoFH Three “orphan” drugs are approved specifically for the management of HoFH, a rare condition caused by biallelic mutations in the major genes causing FH in which patients respond poorly to traditional LDL-lowering medications. Lomitapide is a small-molecule inhibitor of MTP that reduces LDL-C by ~50%, and mipomersen is an antisense oligonucleotide against apoB that reduces LDL-C by ~25%. Both of these drugs reduce hepatic VLDL production and thus LDL-C levels; however, due to their mechanism of action, each drug causes an increase in hepatic fat, the long-term consequences of which are unknown. In addition, lomitapide is associated with gastrointestinal-related side effects, and mipomersen is associated with skin reactions and flulike symptoms. Finally, an antibody inhibitor of ANGPTL3, evinacumab, was approved in 2021 for the treatment of HoFH. In a phase 3 trial, an intravenous infusion every 4 weeks reduced LDL-C levels in patients with HoFH by ~50% and was well toler ated. One of these three drugs should be strongly considered in HoFH patients after a trial of a high-intensity statin, and possibly a PCSK9 inhibitor, is shown to be insufficient to reduce LDL-C levels. PART 12 Endocrinology and Metabolism LDL Apheresis Patients with severe hypercholesterolemia who cannot reduce their LDL-C to acceptable levels despite optimally tolerated combination drug therapy are candidates for LDL apher esis. In this process, the patient’s plasma is passed over a column that selectively removes the LDL, and the LDL-depleted plasma is returned to the patient. LDL apheresis is indicated for patients on maximally tolerated combination drug therapy (including a PCSK9 inhibitor) who have CHD and a plasma LDL-C level >200 mg/dL or no CHD and a plasma LDL-C level >300 mg/dL; LDL apher esis could be considered in high-risk patients who have an LDL-C

> 160 mg/dL on maximal therapy. ■ ■FURTHER READING Cholesterol Treatment Trialists’ (CTT) Collaboration: Effects of statin therapy on diagnoses of new-onset diabetes and worsening glycaemia in large-scale randomised blinded statin trials: An indi vidual participant data meta-analysis. Lancet Diabetes Endocrinol 12:306, 2024. Hernandez P et al: Clinical management of hypertriglyceridemia in

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The Metabolic Syndrome The metabolic syndrome (syndrome X, insulin resistance syndrome) consists of a constellation of metabolic abnormalities that confer increased risk of cardiovascular disease (CVD) and diabetes mellitus. Evolution of the criteria for the metabolic syndrome since the original definition by the World Health Organization in 1998 reflects growing clinical evidence and analysis by a variety of consensus conferences and professional organizations. The major features of metabolic syndrome include central obesity, hypertriglyceridemia, low levels of highdensity lipoprotein (HDL) cholesterol, hyperglycemia, and hyperten sion (Table 420-1). ■ ■GLOBAL HEALTH/EPIDEMIOLOGY The most challenging feature of the metabolic syndrome to define is waist circumference. Intraabdominal circumference (visceral adipose tissue) is most strongly related to insulin resistance and risk of diabetes and CVD, and for any given waist circumference, the distribution of adipose tissue between subcutaneous (SC) and visceral depots varies substantially. Thus, within and between populations, there is a lesser versus greater risk at the same waist circumference. These differences in populations reflect the range of waist circumferences considered to confer risk in different geographic locations (Table 420-1). The prevalence of the metabolic syndrome varies around the world, in part reflecting the age and ethnicity of the populations studied and the diagnostic criteria applied. In general, the prevalence of metabolic syndrome increases with age. The prevalence of metabolic syndrome in the U.S. adult population meeting the criteria of the National Cho lesterol Education Program (NCEP) and Adult Treatment Panel III (ATPIII) is ~35%. Greater global industrialization is associated with rising rates of obesity and related increase in the prevalence of the metabolic syndrome, especially as the population ages. Using National Health and Nutrition Examination Survey (NHANES) data from 1999–2018, the prevalence of metabolic syn drome in 28,049 adults in the United States was 33.4%. The highest

prevalence was age-dependent with reduction by age 80 among all sub groups, i.e., from 19.5% among those aged 20–39 years to 48.6% among those aged ≥60 years. Importantly, the rising prevalence and severity of obesity among children reflect features of the metabolic syndrome in a younger population, now estimated to be 12 and 30% among obese and overweight children, respectively. The frequency distribution of different components of metabolic syndrome for the U.S. population (NHANES III) and the Guangdong Gut Microbiome Project of China is summarized in Fig. 420-1. Note the major differences in the U.S. population compared to Han Chinese. Moreover, within the United States, abdominal obesity appears equally prevalent in all U.S. races, whereas the prevalence of age-dependent other components differs as shown in Fig. 420-1. Increases in hyper glycemia were most evident in the 2017–2018 sample, whereas central obesity, low HDL cholesterol, and hypertension prevalence have been relatively constant, while levels of triglycerides (defined as >150 mg/dL) have progressively decreased. ■ ■RISK FACTORS Overweight/Obesity Metabolic syndrome was first described in the early twentieth century; however, the worldwide overweight/ obesity epidemic has recently been the force driving its increasing recognition. Central adiposity is a key feature of the syndrome, and the syndrome's prevalence reflects the strong relationship between waist circumference and increasing adiposity. However, despite the importance of obesity, patients who are of normal weight may also be insulin-resistant and may have metabolic syndrome. This phenotype is particularly evident for populations in India, Southeast Asia, and Central America.

TABLE 420-1 NCEP:ATPIIIa 2001 and Harmonizing Definition Criteria for the Metabolic Syndrome NCEP:ATPIII 2001 HARMONIZING DEFINITIONb Three or more of the following: • Central obesity: waist circumference >102 cm (males), Three of the following: Waist circumference (cm)

> 88 cm (females) • Hypertriglyceridemia: triglyceride level ≥150 mg/dL or Men Women Ethnicity ≥94 ≥80 Europid, sub-Saharan African, Eastern and Middle Eastern specific medication • Low HDLc cholesterol: <40 mg/dL and <50 mg/dL for ≥90 ≥80 South Asian, Chinese, and ethnic South and Central American ≥85 ≥90 Japanese men and women, respectively, or specific medication • Hypertension: blood pressure ≥130 mmHg systolic or • Fasting triglyceride level >150 mg/dL or specific medication • HDL cholesterol level <40 mg/dL and <50 mg/dL for men and women, respectively, or specific medication • Blood pressure >130 mm systolic or >85 mm diastolic or previous diagnosis or specific medication • Fasting plasma glucose level ≥100 mg/dL (alternative indication: drug treatment of elevated glucose levels) ≥85 mmHg diastolic or specific medication • Fasting plasma glucose level ≥100 mg/dL or specific medication or previously diagnosed type 2 diabetes aNational Cholesterol Education Program and Adult Treatment Panel III. bIn this analysis, the following thresholds for waist circumference were used: white men, ≥94 cm; African-American men, ≥94 cm; Mexican-American men, ≥90 cm; white women, ≥80 cm; African-American women, ≥80 cm; Mexican-American women, ≥80 cm. For participants whose designation was "other race—including multiracial," thresholds that were once based on Europid cutoffs (≥94 cm for men and ≥80 cm for women) and on South Asian cutoffs (≥90 cm for men and ≥80 cm for women) were used. For

> participants who were considered “other Hispanic,” the International Diabetes Federation thresholds for ethnic South and Central Americans were used. cHigh-density lipoprotein. Sedentary Lifestyle Physical inactivity and less cardiorespiratory fitness are predictors of CVD events and the related risk of death. Many components of the metabolic syndrome are associated with a sedentary lifestyle, including increased adipose tissue (predominantly central), reduced HDL cholesterol, and increased triglycerides, blood pressure, and glucose in genetically susceptible persons. Compared with indi viduals who watch television or videos or use the computer <1 h daily, those who do so for >4 h daily have a twofold increased risk of the metabolic syndrome. Genetics No single gene explains the complex phenotype called metabolic syndrome. However, using genome-wide association and MetS Abdominal Obesity

Prevalence (%) Prevalence (%) Prevalence (%)

Age (years)

Age (years)

Age (years) Elevated BP Elevated TG Reduced HDL-C

Prevalence (%)

Age (years)

Age (years)

Age (years) Han Chinese Mexican American Non-Hispanic Black Non-Hispanic White FIGURE 420-1 The frequency distribution of the metabolic syndrome for the U.S. population (National Health and Nutrition Examination Survey [NHANES] III) and the Guangdong Gut Microbiome Project of China. The prevalence of metabolic syndrome (MetS) and its components with age across different races. Prevalence was estimated using a SWAN algorithm (shown as dots). The trajectory of the prevalence of MetS with age was fitted by cubic regressions (shown as lines). BP, blood pressure; FPG, fasting plasma glucose; HDL-C, high-density lipid cholesterol; SWAN, sliding window–based algorithm; TG, triglycerides. (Reproduced from R Zhang et al: The racial disparities in the epidemic of metabolic syndrome with increased age: A study from 28,049 Chinese and American adults. Front Public Health 9:797183, 2022.)

The Metabolic Syndrome CHAPTER 420 candidate gene approaches, several genetic variants are associated with metabolic syndrome. Although many of the loci have unknown function, many others relate to body weight and composition, insu lin resistance, and unfavorable disturbances in lipid and lipoprotein metabolism. In general, heritability estimates for each of the metabolic traits exceed 50%. Aging The metabolic syndrome affects nearly 50% of the U.S. population aged >60, and at >60 years of age, women are more often affected. The age dependency of the syndrome’s prevalence is seen in most populations around the world. Elevated FPG

Prevalence (%) Prevalence (%)

Diabetes Mellitus Diabetes mellitus can be included in both the NCEP and the Harmonizing Definitions of metabolic syndrome, but the greatest value of metabolic syndrome, and especially fast ing glucose, is predicting type 2 diabetes. The great majority (~75%) of patients with type 2 diabetes or impaired glucose tolerance have metabolic syndrome. The presence of metabolic syndrome in these populations relates to a higher prevalence of CVD than in patients who have type 2 diabetes or impaired glucose tolerance but do not have the syndrome.

Cardiovascular Disease Individuals with metabolic syndrome are twice as likely to die of CVD as those who do not, and their risk of acute myocardial infarction or stroke is threefold higher. The approxi mate prevalence of metabolic syndrome among patients with coronary heart disease (CHD) is up to 60% in persons >75 years, with a preva lence of ~35% among patients with premature coronary artery disease (age ≤45) and a particularly higher prevalence among women. With appropriate cardiac rehabilitation and changes in lifestyle (e.g., nutrition, physical activity, weight reduction, and—in some cases—pharmacologic therapy), the prevalence of the syndrome can be reduced. PART 12 Endocrinology and Metabolism Lipodystrophy Lipodystrophic disorders in general are associ ated with metabolic syndrome. Moreover, it is quite common for such patients to present with the metabolic syndrome. Both genetic lipodystrophy (e.g., Berardinelli-Seip congenital lipodystrophy, Dun nigan familial partial lipodystrophy) and acquired lipodystrophy (e.g., HIV-related lipodystrophy and in HIV patients receiving certain anti retroviral therapies) may give rise to severe insulin resistance and many of the components of metabolic syndrome. C-III C-II HDL cholesterol B-100 and TG Insulin Small dense LDL VLDL Glucose TNF-α IL-6 CRP FFA Fibrinogen PAI-1 Adiponectin Prothrombotic state FIGURE 420-2 Pathophysiology of the metabolic syndrome. Free fatty acids (FFAs) are released in abundance from an expanded adipose tissue mass. In the liver, FFAs result in increased production of glucose and triglycerides and secretion of very-low-density lipoproteins (VLDLs). Associated lipid/lipoprotein abnormalities include reductions in high-density lipoprotein (HDL) cholesterol and an increased low-density lipoprotein (LDL) particle number. FFAs also reduce insulin sensitivity in muscle by inhibiting insulin-mediated glucose uptake. Associated defects include a reduction in glucose partitioning to glycogen and increased lipid accumulation in triglyceride (TG). The increase in circulating glucose, and to some extent FFAs, increases pancreatic insulin secretion, resulting in hyperinsulinemia. Hyperinsulinemia may result in enhanced sodium reabsorption and increased sympathetic nervous system (SNS) activity and contribute to hypertension, as might higher levels of circulating FFAs. The proinflammatory state is superimposed and contributory to the insulin resistance produced by excessive FFAs. The enhanced secretion of interleukin 6 (IL-6) and tumor necrosis factor α (TNF-α) produced by adipocytes and monocyte-derived macrophages results in more insulin resistance and lipolysis of adipose tissue triglyceride stores to circulating FFAs. IL-6 and other cytokines also enhance hepatic glucose production, VLDL production by the liver, hypertension, and insulin resistance in muscle. Insulin resistance also contributes to increased triglyceride accumulation in the liver (nonalcoholic fatty liver disease). Cytokines and FFAs also increase hepatic production of fibrinogen and adipocyte production of plasminogen activator inhibitor 1 (PAI-1), resulting in a pro-thrombotic state. Higher levels of circulating cytokines stimulate hepatic production of C-reactive protein (CRP). Reduced production of the anti-inflammatory and insulin-sensitizing cytokine adiponectin is also associated with the metabolic syndrome. (Reproduced with permission from RH Eckel et al: The metabolic syndrome. Lancet 365:1415, 2005.)

■ ■ETIOLOGY Insulin Resistance The most accepted and unifying hypothesis to describe the pathophysiology of metabolic syndrome is insulin resis tance, caused systemically by an incompletely understood defect in insulin action (Chap. 415). The onset of insulin resistance is heralded by postprandial hyperinsulinemia, which is followed by fasting hyper insulinemia and ultimately by hyperglycemia. An early major contributor to the development of insulin resistance is an overabundance of circulating fatty acids (Fig. 420-2). Plasma albumin-bound free fatty acids are derived predominantly from adi pose-tissue triglyceride stores released by intracellular lipolytic enzymes. The lipolysis of triglyceride-rich lipoproteins in tissues by lipoprotein lipase also produces free fatty acids. Insulin mediates both anti-lipolysis and the stimulation of lipoprotein lipase in adipose tissue. Of note, the inhibition of lipolysis in adipose tissue is the most sensitive pathway of insulin action. Thus, when insulin resistance develops, increased lipoly sis produces more fatty acids, which further decreases the anti-lipolytic effect of insulin. Excessive fatty acids enhance substrate availability and create insulin resistance by modifying downstream signaling. Fatty acids impair insulin-mediated glucose uptake and are associated with accu mulation of triglycerides in both skeletal and cardiac muscle, whereas increased fatty acid flux increases endogenous glucose production and triglyceride production, accumulation, and secretion in the liver. Reductions in leptin action may also be a pathophysiologic mecha nism to explain metabolic syndrome. Physiologically, leptin reduces appetite, promotes energy expenditure, and enhances insulin sensi tivity. In addition, leptin may regulate cardiac and vascular function through a nitric oxide–dependent mechanism. However, when obesity Hypertension FFA IL-6 SNS Insulin – Glycogen – CO_2 FFA – Triglyceride (intramuscular droplet)

develops, hyperleptinemia ensues, with evidence of leptin resistance in the brain and other tissues resulting in insulin resistance and associ ated inflammation, hyperlipidemia, and a plethora of cardiovascular disorders, such as hypertension, atherosclerosis, CHD, and heart failure. Moreover, a series of adipokines relate to metabolic syndrome. Whereas adiponectin improves insulin sensitivity in adipose tissue and skeletal muscle, visfatin, fetuin-A, resistin, asprosin, and plasminogen activator inhibitor-1 contribute to insulin resistance and systemic glu cose intolerance. The oxidative stress hypothesis provides a unifying theory for aging and the predisposition to metabolic syndrome. In studies of insulinresistant individuals with obesity or type 2 diabetes, the offspring of persons with type 2 diabetes, and the elderly, a defect in mitochondrial oxidative phosphorylation leads to the accumulation of triglycer ides and related lipid molecules in muscle, liver, and other tissues, i.e., β-cells. The gut microbiome has emerged as an important contributor to the development of obesity and related metabolic disorders, includ ing inflammation and components of metabolic syndrome. Although the mechanisms remain uncertain, an increased ratio of Firmicutes/ Bacteroidetes species in addition to genetic predisposition, diet, and bile acid metabolism are associated with and may play an etiologic role in metabolic syndrome. Increased Waist Circumference Waist circumference is an impor tant component of the most recent and frequently applied diagnostic cri teria for metabolic syndrome. However, measuring waist circumference does not reliably distinguish increases in SC abdominal adipose tissue from that in intra-abdominal or visceral fat; this distinction requires dual X-ray absorptiometry (DEXA), computed tomography (CT), or magnetic resonance imaging (MRI) to discriminate. With increases in visceral adipose tissue, adipose tissue–derived free fatty acids reach the liver more readily. In contrast, increases in abdominal SC fat release lipolysis products into the systemic circulation and therefore have fewer direct effects on hepatic metabolism. Relative increases in visceral versus SC adipose tissue with increasing waist circumference in Asians and Asian Indians may explain the

greater prevalence of metabolic syn drome in those populations than in African Americans, in whom SC fat predominates. It is also possible that visceral fat is a marker for—but not the source of—excess postprandial free fatty acids in obesity. Dyslipidemia (See also Chap. 419) In general, free fatty acid flux from adipose tissue to the liver results in increased production of apolipoprotein (apo) B–containing, triglyceride-rich, very-low-density lipoproteins (VLDLs). The direct effect of insulin on this process is complex, but hypertriglyceridemia is an excellent marker of the insulin-resistant condition. Not only is hypertriglyceridemia a feature of metabolic syndrome, but patients with metabolic syndrome have elevated levels of apoC-III carried on VLDLs and other lipoproteins. This increase in apoC-III is inhibitory to lipoprotein lipase, reducing triglyceride-rich lipoprotein remnant removal, further contributing to hypertriglyceridemia, and confers more risk for atherosclerotic cardio vascular disease (ASCVD). The other major lipoprotein disturbance in metabolic syndrome is a reduction in HDL cholesterol. This reduction is a consequence of changes in HDL composition and metabolism. In the presence of hypertriglyceridemia, a decrease in the cholesterol content of HDL is a consequence of reduced cholesteryl ester content of the lipoprotein core in combination with cholesteryl ester transfer protein–mediated alterations in triglycerides that make the HDL particle small and dense. This change in lipoprotein composition also results in increased clearance of HDL from the circulation. These changes in HDL have a relationship to insulin resistance that is probably indirect, occurring in concert with the changes in triglyceride-rich lipoprotein metabolism. In addition to HDLs, low-density lipoproteins (LDLs) have altera tions in composition in metabolic syndrome. With fasting serum triglycerides at >2.0 mM (~180 mg/dL), there is usually a predomi nance of small dense LDLs, which are thought to be more atherogenic, although their association with hypertriglyceridemia and low HDLs makes their independent contribution to ASCVD difficult to assess.

Individuals with hypertriglyceridemia often have increases in choles terol content of both VLDL1 and VLDL2 subfractions and in LDL par ticle number. Both lipoprotein changes may contribute to atherogenic risk in patients with metabolic syndrome. Glucose Intolerance (See also Chap. 415) Defects in insulin action in metabolic syndrome lead to impaired suppression of endoge nous glucose production by the liver (and kidney) and reduced glucose uptake and metabolism in insulin-sensitive tissues—i.e., muscle and adipose tissue. There is a strong relationship between impaired fasting glucose or impaired glucose tolerance and insulin resistance in stud ies of humans, nonhuman primates, and rodents. To compensate for defects in insulin action, insulin secretion and/or clearance increases or decreases, respectively, so that euglycemia remains. Ultimately, this compensatory mechanism fails because of defects in insulin secretion, resulting in progression from impaired fasting glucose and/or impaired glucose tolerance to type 2 diabetes mellitus. Hypertension The relationship between insulin resistance and hypertension is well established. Paradoxically, under normal physi ologic conditions, insulin-mediated increases in nitric oxide cause vaso dilation with secondary effects on sodium reabsorption in the kidney. However, in the setting of insulin resistance, the vasodilatory effect of insulin is lost but the renal effect on sodium reabsorption is preserved. Sodium reabsorption is increased in Caucasians with metabolic syn drome but not in Africans or Asians. Insulin also increases the activity of the sympathetic nervous system, an effect that is preserved in the setting of insulin resistance. Insulin resistance is also associated with pathwayspecific impairment in phosphatidylinositol-3-kinase signaling. In the endothelium, this impairment may cause an imbalance between the production of nitric oxide and the secretion of endothelin 1, with a consequent decrease in blood flow. In addition, increases in angioten sinogen gene expression in adipose tissue of obese subjects results

in increases in circulating angiotensin II and vasoconstriction. Although these mechanisms are provocative, the inadequate evaluation of insulin action by measurement of fasting insulin levels or by homeostasis model assessment shows that insulin resistance contributes only partially to the increased prevalence of hypertension in metabolic syndrome.

The Metabolic Syndrome CHAPTER 420 Another possible mechanism underlying hypertension in metabolic syndrome is the vasoactive role of perivascular adipose tissue. Reactive oxygen species released by NADPH oxidase impair endothelial func tion and result in local vasoconstriction. Other paracrine effects such as leptin or other proinflammatory cytokines released from adipose tis sue, such as tumor necrosis factor α (TNF-α), may also be important. Hyperuricemia is another consequence of insulin resistance in metabolic syndrome. There is growing evidence not only that uric acid is associated with hypertension but also that reduction of uric acid normalizes blood pressure in hyperuricemic adolescents with hyper tension. The mechanism appears to be in part related to an adverse effect of uric acid on nitric oxide synthase in the macula densa of the kidney and stimulation of the renin-angiotensin-aldosterone system. Proinflammatory Cytokines The increases in proinflammatory cytokines—including interleukins 1, 6, and 18; resistin; TNF-α; and the systemic biomarker C-reactive protein—reflect overproduction by the expanded adipose tissue mass (Fig. 420-2). Adipose tissue–derived macrophages may be the primary source of proinflammatory cytokines locally and in the systemic circulation. It remains unclear, however, how much of the insulin resistance is caused by the paracrine effects of these cytokines and how much by the endocrine effects. Adiponectin Adiponectin is an anti-inflammatory cytokine pro duced exclusively by adipocytes. Adiponectin enhances insulin sensi tivity and inhibits many steps in the inflammatory process. In the liver, adiponectin inhibits the expression of gluconeogenic enzymes and the rate of glucose production. In muscle, adiponectin increases glucose transport and enhances fatty acid oxidation, partially through the activation of AMP kinase. Reductions in adiponectin levels are com mon in metabolic syndrome. The relative contributions of adiponectin deficiency and overabundance of the proinflammatory cytokines are unclear.

■ ■CLINICAL FEATURES

Symptoms and Signs Metabolic syndrome typically is not associ ated with symptoms. On physical examination, waist circumference and blood pressure are often elevated. The presence of either or both signs should prompt the clinician to search for other biochemical abnormalities that may be associated with metabolic syndrome. Much less frequently, lipoatrophy or acanthosis nigricans is present on exami nation. Because these physical findings characteristically are associated with severe insulin resistance, other components of metabolic syn drome are much more common. Associated Diseases • CARDIOVASCULAR DISEASE The rela tive risk for new-onset CVD in patients with metabolic syndrome who do not have diabetes averages 1.5- to 3-fold. However, in INTERHEART, a study of 26,903 subjects from 52 countries, the risk for acute myocardial infarction in subjects with metabolic syndrome (World Health Organization or International Diabetes Federation definition) is comparable to that conferred by some, but not all, of the component risk factors. Diabetes mellitus (odds ratio [OR], 2.72) and hypertension (OR, 2.60) are stronger than other risk factors. Although congestive heart failure and metabolic syndrome can occur together, typically this consequence is secondary to metabolic syn drome–related ASCVD or hypertension. Metabolic syndrome is also associated with increases in the risk for stroke, peripheral vascular disease, and Alzheimer’s disease. However, as for myocardial infarc tion, the risk beyond the

additive role of the components of metabolic syndrome remains debatable. In the Reasons for Geographic and Racial Differences in Stroke (REGARDS) cohort, an observational study of black and white adults ≥45 years old across the United States, there were 9741 participants, and 41% had metabolic syndrome. After adjustment for multiple confounders, metabolic syndrome was asso ciated with increases in high-sensitivity C-reactive protein (hsCRP), and this relationship was associated with a 1.34 relative risk for allcause mortality, but <50% of deaths were from CVD. The populationattributable risk was 9.5% for metabolic syndrome alone and 14.7% for both metabolic syndrome and increased hsCRP. The relationship of metabolic syndrome and hsCRP to mortality was greater for whites than blacks. PART 12 Endocrinology and Metabolism TYPE 2 DIABETES Overall, the risk for type 2 diabetes among patients with metabolic syndrome is increased three- to fivefold. In the Framingham Offspring Study's 8-year follow-up of middle-aged par ticipants, the population-attributable risk of metabolic syndrome for developing type 2 diabetes was 62% among men and 47% among women, yet increases in fasting plasma glucose explained most, if not all, of this increased risk. Other Associated Conditions In addition to the features specifi cally used to define metabolic syndrome, other metabolic alterations are secondary to or accompany insulin resistance. Those alterations include increases in apoB and apoC-III, uric acid, prothrombotic factors (fibrinogen, plasminogen activator inhibitor 1), serum viscos ity, asymmetric dimethylarginine, homocysteine, white blood cell count, proinflammatory cytokines, C-reactive protein, urine albumin/ creatinine ratio, metabolic-associated fatty liver disease (MAFLD) and/or nonalcoholic steatohepatitis (NASH), polycystic ovary syndrome, and obstructive sleep apnea. METABOLIC-ASSOCIATED FATTY LIVER DISEASE MAFLD has become the most common liver disease, in part a consequence of the insulin resistance of metabolic syndrome. The mechanism relates to increases in free fatty acid flux and reductions in intrahepatic fatty acid oxidation with resultant increases in triglyceride biosynthesis and hepatocel lular accumulation, with variable inflammation and oxidative stress. The more serious Metabolic dysfunction-associated steatohepatitis (MASH), a consequence of MAFLD in some patients and a precursor of cirrhosis and end-stage liver disease, includes a more substantial proinflammatory contribution. MAFLD affects ~10% of the nonobese population and up to 65% of patients with metabolic syndrome; over half of these patients have metabolic dysfunction-associated

steatohepatitis (MASH). As the prevalence of overweight/obesity and metabolic syndrome increases, NASH may become one of the more common causes of end-stage liver disease and hepatocellular carci noma. Increasingly, studies have shown that MAFLD is related inde pendently to CVD, especially coronary artery disease. HYPERURICEMIA (See also Chap. 384) Hyperuricemia reflects defects in insulin action on the renal tubular reabsorption of uric acid and may contribute to hypertension through its effect on the endothelium. An increase in asymmetric dimethylarginine, an endogenous inhibitor of nitric oxide synthase, also relates to endothelial dysfunction. In addition, increases in the urine albumin/creatinine ratio may relate to altered endothelial pathophysiology in the insulin-resistant state. POLYCYSTIC OVARY SYNDROME (See also Chap. 404) Polycystic ovary syndrome is highly associated with insulin resistance (50–80%) and metabolic syndrome, with a prevalence of the syndrome between 12 and 60% based on phenotypes D through A. OBSTRUCTIVE SLEEP APNEA (See also Chap. 33) Obstructive sleep apnea is commonly associated with obesity, hypertension, increased circulating proinflammatory cytokines, impaired glucose tolerance, and insulin resistance. In fact, obstructive sleep apnea may predict metabolic syndrome, even in the absence of excess adiposity. Moreover, when biomarkers of insulin resistance are compared between patients with obstructive sleep apnea and weight-matched

controls, insulin resistance is found to be more severe in those with apnea. Continu ous positive airway pressure treatment improves insulin sensitivity in patients with obstructive sleep apnea. ■ ■DIAGNOSIS The diagnosis of metabolic syndrome relies on fulfillment of the cri teria listed in Table 420-1, as assessed using tools at the bedside and in the laboratory. The medical history should include evaluation of symptoms for obstructive sleep apnea in all patients and polycystic ovary syndrome in premenopausal women. Family history will help determine the risk for CVD and diabetes mellitus. Blood pressure and waist circumference measurements provide information necessary for the diagnosis. Laboratory Tests Measurement of fasting lipids and glucose is needed in determining whether metabolic syndrome is present. The measurement of additional biomarkers associated with insulin resistance can be individualized. Such tests might include those for apoB, hsCRP, fibrinogen, uric acid, urinary albumin/creatinine ratio, and liver function. A sleep study should be performed if symptoms of obstructive sleep apnea are present. If polycystic ovary syndrome is suspected based on clinical features and anovulation, testosterone, luteinizing hormone, and follicle-stimulating hormone should be mea sured. MAFLD can be further assessed by the MAFLD fibrosis score (FIB4) or elastography. TREATMENT The Metabolic Syndrome LIFESTYLE (SEE ALSO CHAP. 414) Obesity, particularly abdominal, is the driving force behind meta bolic syndrome. Thus, weight reduction is the primary approach to the disorder. With at least 5% and more so with 10% weight reduc tion, improvement in insulin sensitivity results in favorable modi fications in many components of 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 regains after successful weight reduction underscores the need for long-lasting behavioral changes.

Diet Before prescribing a weight-loss diet, it is important to empha size that it has taken the patient a long time to develop an expanded fat mass; thus, the correction need not occur quickly. Given, in gen eral, that ~3500 kcal = 1 lb of adipose tissue, an ~500-kcal restriction daily equates to weight reduction of 1 lb per week. Diets restricted in carbohydrate typically provide a more 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 the chosen diet. Moreover, there is concern about low-carbohydrate diets enriched in saturated fat, particularly for patients at risk for ASCVD. Therefore, a high-quality dietary pattern—i.e., a diet enriched in fruits, vegetables, whole grains, lean poultry, and fish—should be encouraged to maxi mize overall health benefit. Physical Activity Before prescribing a physical activity program to patients with 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 moderate- to high-intensity daily activity is required to achieve this goal. Even if an overweight or obese adult is unable to undertake this level of activity, a health benefit will follow from at least 30 min of moderate-intensity activ ity daily. The caloric value of 30 min of a variety of activities can be found at https://www.health.harvard.edu/diet-and-weight-loss/ calories-burned-in-30-minutes-of-leisure-and-routine-activities. Of note, a variety of routine activities, such as gardening, walking, and

housecleaning, require moderate caloric expenditure. Thus, physi cal activity should 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 activ ity that predicts sufficient weight loss that benefits metabolic health. The subsequent challenge is the duration of the program because weight regain so often follows successful weight reduction. Improved long-term outcomes often follow a variety of methods, such as a personal or group counselor, the Internet, social media, and telephone follow-up to maintain contact between providers and patients. Obesity (See also Chap. 414) In some patients with metabolic syndrome, treatment options need to extend beyond lifestyle intervention. Weight-loss drugs come in two major classes: appe tite suppressants and absorption inhibitors. Appetite suppressants approved by the U.S. Food and Drug Administration (FDA) include phentermine (for short-term use [3 months] only) as well as phen termine/topiramate, naltrexone/bupropion, high-dose (3.0 mg) liraglutide (rather than 1.8 mg, the maximum for treatment of type 2 diabetes), and semaglutide (2.4 mg), which are approved without restrictions on the duration of therapy. In clinical trials, the phentermine/topiramate extended-release combination resulted in ~8% weight loss relative to placebo in 50% of patients. Side effects include palpitations, headache, paresthesias, constipation, and insomnia. Naltrexone/bupropion extended release reduces body weight by ≥10% in ~20% of patients; however, the drug combina tion is contraindicated in patients with seizure disorders or any condition that predisposes to seizures. Naltrexone/bupropion also increases pulse and blood pressure and should not be given to patients with uncontrolled hypertension. High-dose liraglutide, a glucagon-like peptide 1 (GLP-1) receptor agonist, results in ~6% weight loss relative to placebo with ~33% of patients with

> 10% weight loss. Common side effects are limited to the upper gastrointestinal tract, including nausea and, less frequently, emesis. Semaglutide (2.4 mg weekly) has been shown to produce an average weight loss of 14.9% over 68 weeks. Tirzepatide, a novel glucosedependent insulinotropic polypeptide (GIP) and GLP-1 receptor

agonist, has been tested for 72 weeks in participants with a mean body weight of 104.8 kg and mean body mass index (BMI) of 38.0 kg/m2, with 94.5% of patients with a BMI of ≥30 kg/m2. Participants expe rienced a dose-dependent reduction in weight ranging from –15.0% with 5 mg of tirzepatide weekly to 20.9% with the 15-mg dose. Benefits of GLP-1 receptor agonists on MAFLD are also notewor thy, but not yet FDA approved.

Orlistat inhibits fat absorption by ~30% and is moderately effec tive compared with placebo (~4% more weight loss). Moreover, orlistat reduced 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 to take because of oily leak age per rectum. In general, for all weight-loss drugs, greater weight reduction leads to greater improvement in metabolic syndrome components, including the conversion from prediabetes to type 2 diabetes. The Metabolic Syndrome CHAPTER 420 Metabolic or bariatric surgery is an important option for patients with metabolic syndrome who have a BMI >40 kg/m2 or >35 kg/m2 with comorbidities. An evolving application for metabolic surgery includes patients with a BMI as low as 30 kg/m2 and type 2 diabetes. Gastric bypass or vertical

sleeve gastrectomy results in dramatic weight reduction and improvement in most features of metabolic syndrome. A survival benefit with gastric bypass has also been realized. LDL CHOLESTEROL (SEE ALSO CHAP. 419) The rationale for the development of criteria for metabolic syn drome by NCEP was to go beyond LDL cholesterol in identifying and reducing the risk of ASCVD. The working assumption by the panel was that LDL cholesterol goals had already been achieved and that increasing evidence supports a linear reduction in ASCVD events because of progressive lowering of LDL cholesterol with statins with subsequent benefit using additional LDL cholesterol– lowering agents. The 2019 American College of Cardiology (ACC)/ American Health Association (AHA) Cholesterol Guidelines have no specific recommendations for patients with metabolic syndrome; however, they recommend that patients aged 20–75 years with LDL cholesterol levels ≥190 mg/dL should use a high-intensity statin (e.g., atorvastatin 40–80 mg or rosuvastatin 20–40 mg daily) and those with type 2 diabetes aged 40–75 years should use a moderateintensity statin and, if or when risk estimate is high, a high-intensity statin. For patients with metabolic syndrome but without diabe tes, the 10-year ASCVD risk estimator should be employed, and patients with a risk ≥7.5% and ≤20% or persons aged 20–59 with elevated lifetime risk should have a discussion with their provider about initiating statin therapy for primary prevention of ASCVD. A coronary calcium score may help in making this decision. Diets restricted in saturated fats (<6% of calories) and trans fats (as few as possible) should be applied aggressively. Although evidence is controversial, dietary cholesterol can also be restricted. If LDL cholesterol remains elevated, pharmacologic intervention is needed. Based on substantial evidence, treatment with statins, which lower LDL cholesterol by 15–60%, is the first-choice medi cation 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, but myopathy occurs in ~10–20% 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%. Bempedoic acid alone or in combination with ezetimibe is another option, with up to a 35% lowering of LDL cholesterol with the combination. Bempedoic acid can increase plasma uric acid. Proprotein convertase subtilisin/ kexin type 9 (PCSK9) inhibitors are potent LDL cholesterol–lowering drugs (~45–60%) but are not needed for most patients with meta bolic syndrome. Of course, if these patients also have familial hypercholesterolemia or insufficient LDL cholesterol lowering on statins with or without ezetimibe, a PCSK9 inhibitor should be considered. The bile acid sequestrants cholestyramine, colestipol,

and colesevelam may be more effective than ezetimibe alone, but because they can increase triglyceride levels, they must be used with caution in patients with metabolic syndrome when fasting triglycer ides are >300 mg/dL. Side effects include gastrointestinal symptoms (palatability, bloating, belching, constipation, anal irritation). Nico tinic acid has similar LDL cholesterol–lowering capabilities (<20%); however, it may be associated with multiple adverse effects. Fibrates are best employed to lower LDL cholesterol when triglycerides are not elevated. Fenofibrate may be more effective than gemfibrozil in this setting.

TRIGLYCERIDES (SEE ALSO CHAP. 419) The 2019 ACC/AHA Cholesterol Guidelines stated that fasting triglycerides >500 mg/dL should be treated to prevent more serious hypertriglyceridemia and pancreatitis. Although a fasting triglyc eride value of >150 mg/dL is a component of metabolic syndrome, post hoc analyses of multiple fibrate trials have not suggested a triglyceride-related reduction in the primary ASCVD outcome in patients (with or without concomitant statin therapy)

with fasting triglycerides >200 mg/dL, often in the setting of reduced levels of HDL cholesterol. It remains uncertain whether triglycerides cause ASCVD or if levels are just associated with increased ASCVD risk. PART 12 Endocrinology and Metabolism A fibrate (gemfibrozil or fenofibrate) is one drug class 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 gem fibrozil. In the Veterans Affairs HDL Intervention Trial, gemfibrozil was administered to men with known CHD and levels of HDL choles terol <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 hav ing metabolic syndrome. Of note, the degree of triglyceride lowering in this trial or other fibrate trials did not predict benefit. Other drugs that lower triglyceride levels include statins, nico tinic acid, and prescription omega-3 fatty acids. For this purpose, an intermediate or high dose of the “more potent” statins (atorvas tatin, rosuvastatin) is needed. The effect of nicotinic acid on fasting triglycerides is dose related and ~20–35%, an effect that is less pro nounced than that of fibrates. In patients with metabolic syndrome and diabetes, nicotinic acid may increase fasting glucose levels, and clinical trials with nicotinic acid plus a statin have failed to reduce ASCVD events. Prescriptions of omega-3 fatty acid preparations that include high doses of eicosapentaenoic acid (EPA) with or without docosahexaenoic acid (DHA) (~1.5–4.5 g/d) lower fast ing triglyceride levels by ~25–40%. The two omega-3 randomized controlled trials associated with ASCVD risk reduction, JELIS and REDUCE-IT, used EPA only, whereas STRENGTH, which was ter minated prematurely because of futility, used EPA plus DHA. Here, no drug interactions with fibrates or statins occur, and the main side effect of their use is eructation with a fishy taste. Freezing the nutraceutical can partially block this unpleasant side effect. Impor tantly, lowering triglycerides with any of the pharmaceuticals has not been proven to be an independent predictor of CVD outcomes. HDL CHOLESTEROL (SEE ALSO CHAP. 419) Very few lipid-modifying compounds increase HDL cholesterol lev els. Statins, fibrates, and bile acid sequestrants have modest effects (5–10%), whereas ezetimibe and omega-3 fatty acids have no effect. Nicotinic acid is the only currently available drug with predictable HDL cholesterol–raising properties. The response is dose related, and nicotinic acid can increase HDL cholesterol by up to 30% above baseline. After several trials of nicotinic acid versus placebo in statin-treated patients, there is no evidence that raising HDL cholesterol with nicotinic acid beneficially affects ASCVD events in patients with or without metabolic syndrome. BLOOD PRESSURE (SEE ALSO CHAP. 288) The direct relationship between blood pressure and all-cause mor tality rate has been well established in studies comparing patients

with hypertension (>140/90 mmHg), patients with prehypertension (>120/80 mmHg but <140/90 mmHg), and individuals with normal blood pressure (<120/80 mmHg). In patients who have metabolic syndrome without diabetes, the best choice for the initial antihy pertensive medication is an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin II receptor blocker, as these two classes of drugs are effective and well tolerated. Additional agents include a diuretic, calcium channel blocker, beta blocker, and mineralocorti coid inhibitor, such as the recent FDA-approved mineralocorticoid receptor antagonist finerenone. In all patients with hypertension, a sodium-restricted dietary pattern enriched in fruits and vegetables, whole grains, and low-fat dairy products should be advocated. Home monitoring of blood pressure may assist in maintaining good blood pressure control. IMPAIRED FASTING GLUCOSE (SEE ALSO CHAP. 415) In patients with metabolic syndrome and type 2 diabetes, aggressive glycemic control may favorably modify fasting levels of triglyc erides and/or HDL cholesterol. In patients with impaired fasting glucose who

do not have diabetes, a lifestyle intervention that includes weight reduction, dietary saturated fat restriction, and increased physical activity has been shown to reduce the incidence of type 2 diabetes. Metformin also reduces the incidence of dia betes, although the effect is less pronounced than that of lifestyle intervention. INSULIN RESISTANCE (SEE ALSO CHAP. 416) Several drug classes (biguanides, thiazolidinediones [TZDs]) increase insulin sensitivity. Because insulin resistance is the primary pathophysiologic mechanism for metabolic syndrome, representa tive drugs in these classes reduce its prevalence. Both metformin and TZDs enhance insulin action in the liver and suppress endog enous glucose production. TZDs, but not metformin, also improve insulin-mediated glucose uptake in muscle and adipose tissue. In a meta-analysis of nine trials involving 12,026 participants, the TZD pioglitazone versus placebo was associated with reduction in ASCVD events in patients with insulin resistance (metabolic syn drome), prediabetes, and type 2 diabetes. However, adverse effects including weight gain, bone fracture, and congestive heart failure with/or without edema were seen. Benefit of TZDs has been seen in patients with MAFLD, and with metformin in women with polycystic ovary syndrome, and both drug classes have been shown to reduce markers of inflammation. GLP-1 receptor agonists also improve insulin sensitivity, which is related to the amount of weight reduction. ■ ■FURTHER READING Alberti KG et al: Harmonizing the metabolic syndrome: A joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federa tion; International Atherosclerosis Society; and International Asso ciation for the Study of Obesity. Circulation 120:1640, 2009. Brown AE, Walker M: Genetics of insulin resistance and the meta bolic syndrome. Curr Cardiol Rep 18:75, 2016. Dobrowolski P et al: Metabolic syndrome: A new definition and management guidelines. Arch Med Sci 5:1, 2022. Eckel RH et al: The metabolic syndrome. Lancet 365:1415, 2005. Fahed G et al: Metabolic syndrome: Update on pathophysiology and management in 2021. Int J Mol Sci 23: 786, 2022. Genser L et al: Obesity, type 2 diabetes, and the metabolic syndrome: Pathophysiologic relationships and guidelines for surgical interven tion. Surg Clin North Am 96:681, 2016. Lechner K et al: High-risk atherosclerosis and metabolic phenotype: The roles of ectopic adiposity, atherogenic dyslipidemia, and inflam mation. Metab Syndr Relat Disord 18:176, 2020. Neeland IJ et al: Visceral and ectopic fat, atherosclerosis, and cardio metabolic disease: A position statement. Lancet Diabetes Endocrinol 7:715, 2019.

Revision #1
Created 2026-01-06 16:35:25 UTC by Omar Ayman
Updated 2026-01-06 16:35:26 UTC by Omar Ayman