clear evidence that fibrates reduce CVD risk; however, post hoc analyses of several studies demonstrated that patients with baseline triglyceride levels >200 mg/dL and HDL cholesterol levels <35 mg/dL did benefit.

Other drugs that lower triglyceride levels include statins, nicotinic acid, and—in high doses—omega-3 fatty acids. For this purpose, an intermediate or high dose of the "more potent" statins (atorvastatin, rosuvastatin) is needed. The effect of nicotinic acid on fasting triglycerides is dose related and ~20–35%, an effect that is less pronounced than that of fibrates. In patients with the metabolic syndrome and diabetes, nicotinic acid may increase fasting glucose levels. Omega-3 fatty acid preparations that include high doses of docosahexaenoic acid plus eicosapentaenoic acid (~1.5–4.5 g/d) or eicosapentaenoic acid alone lower fasting triglyceride levels by ~30–40%. No drug interactions with fibrates or statins occur, and the main side effect of their use is eructation with a fishy taste. This taste can be partially blocked by ingestion of the nutraceutical after freezing. Clinical trials of nicotinic acid or high-dose omega-3 fatty acids in patients with the metabolic syndrome have not been reported.

HDL CHOLESTEROL (SEE ALSO CHAP. 421)

Very few lipid-modifying compounds increase HDL cholesterol levels. 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 ~30% above baseline. After several trials of nicotinic acid versus placebo in statin-treated patients, there is still no evidence that raising HDL with nicotinic acid beneficially affects CVD events in patients with or without the metabolic syndrome.

BLOOD PRESSURE (SEE ALSO CHAP. 298)

The direct relationship between blood pressure and all-cause mortality rate has been well established in studies comparing patients with hypertension (>140/90 mmHg), patients with pre-hypertension (>120/80 mmHg but <140/90 mmHg), and individuals with normal blood pressure (<120/80 mmHg). In patients who have the metabolic syndrome without diabetes, the best choice for the initial antihypertensive medication is an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin II receptor blocker, as these two classes of drugs appear to reduce the incidence of new-onset type 2 diabetes. 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. 417)

In patients with the metabolic syndrome and type 2 diabetes, aggressive glycemic control may favorably modify fasting levels of triglycerides and/or HDL cholesterol. In patients with impaired fasting glucose who do not have diabetes, a lifestyle intervention that includes weight reduction, dietary fat restriction, and increased physical activity has been shown to reduce the incidence of type 2 diabetes. Metformin also reduces the incidence of diabetes, although the effect is less pronounced than that of lifestyle intervention.

INSULIN RESISTANCE (SEE ALSO CHAP. 418)

Several drug classes (biguanides, thiazolidinediones [TZDs]) increase insulin sensitivity. Because insulin resistance is the primary pathophysiologic mechanism for the metabolic syndrome, representative drugs in these classes reduce its prevalence. Both metformin and TZDs enhance insulin action in the liver and suppress endogenous glucose production. TZDs, but not metformin, also improve insulin-mediated glucose uptake in muscle and adipose tissue. Benefits of both drugs have been seen in patients with nonalcoholic fatty liver disease and polycystic ovary syndrome, and the drugs have been shown to reduce markers of inflammation.

SECTION 4 DISORDERS OF BONE AND MINERAL METABOLISM

423 Bone and Mineral Metabolism in Health and Disease

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BONE STRUCTURE AND METABOLISM

Bone is a dynamic tissue that is remodeled constantly throughout life. The arrangement of compact and cancellous bone provides strength and density suitable for both mobility and protection. In addition, bone provides a reservoir for calcium, magnesium, phosphorus, sodium, and other ions necessary for homeostatic functions. Bone also hosts and regulates hematopoiesis by providing niches for hematopoietic cell proliferation and differentiation. The skeleton is highly vascular and receives about 10% of the cardiac output. Remodeling of bone is accomplished by two distinct cell types: osteoblasts produce bone matrix, and osteoclasts resorb the matrix.

The extracellular components of bone consist of a solid mineral phase in close association with an organic matrix, of which 90–95% is type I collagen (Chap. 427). The noncollagenous portion of the organic matrix is heterogeneous and contains serum proteins such as albumin as well as many locally produced proteins, whose functions are incompletely understood. Those proteins include cell attachment/signaling proteins such as thrombospondin, osteopontin, and fibronectin; calcium-binding proteins such as matrix gla protein and osteocalcin; and proteoglycans such as biglycan and decorin. Some of the proteins organize collagen fibrils; others influence mineralization and binding of the mineral phase to the matrix.

The mineral phase is made up of calcium and phosphate and is best characterized as a poorly crystalline hydroxyapatite. The mineral phase of bone is deposited initially in intimate relation to the collagen fibrils and is found in specific locations in the "holes" between the collagen fibrils. This architectural arrangement of mineral and matrix results in a two-phase material well suited to withstand mechanical stresses. The organization of collagen influences the amount and type of mineral phase formed in bone. Although the primary structures of type I collagen in skin and bone tissues are similar, there are differences in posttranslational modifications and distribution of intermolecular cross-links. The holes in the packing structure of the collagen are larger in mineralized collagen of bone and dentin than in unmineralized collagens such as those in tendon. Single amino acid substitutions in the helical portion of either the α1 (*COL1A1*) or α2 (*COL1A2*) chains of type I collagen disrupt the organization of bone in osteogenesis imperfecta. The severe skeletal fragility associated with this group of disorders highlights the importance of the fibrillar matrix in the structure of bone (Chap. 427).

Osteoblasts synthesize and secrete the organic matrix and regulate its mineralization. They are derived from cells of mesenchymal origin (Fig. 423-1*A*). Active osteoblasts are found on the surface of newly