TABLE 364-2 MEDICATIONS ASSOCIATED WITH HEPATIC STEATOSIS

- Cytotoxic and cytostatic drugs
  - L-Asparaginase
  - Azacitidine
  - Azaserine
  - Bleomycin
  - Methotrexate
  - Puromycin
  - Tetracycline
  - Doxycycline
- Metals
  - Antimony
  - Barium salts
  - Chromates
  - Phosphorus
  - Rare earths of low atomic number
  - Thallium compounds
  - Uranium compounds
- Other drugs and toxins
  - Amiodarone
  - 4,4′-Diethylaminoethoxyhexesterol
  - Ethionine
  - Ethyl bromide
  - Estrogens
  - Glucocorticoids
  - Highly active antiretroviral therapy
  - Hydralazine
  - Hypoglycin
  - Orotate
  - Perhexiline maleate
  - Safrole
  - Tamoxifen

prolongation) or portal hypertension (e.g., thrombocytopenia) and stigmata of portal hypertension on physical examination (e.g., spider angiomata, palmar erythema, splenomegaly, ascites, clubbing, encephalopathy) suggest a diagnosis of advanced NAFLD. Currently, however, liver biopsy is the gold standard for establishing the severity of liver injury and fibrosis because it is both more sensitive and specific than these other tests for establishing NAFLD severity. Although invasive, liver biopsy is seldom complicated by serious adverse sequelae such as significant bleeding, pain, or inadvertent puncture of other organs and thus is relatively safe. However, biopsy suffers from potential sampling error unless tissue cores of 2 cm or longer are acquired. Also, examination of tissue at a single point in time is not reliable for determining whether the pathologic processes are progressing or regressing. The risk of serial liver biopsies within short time intervals is generally deemed as unacceptable outside of research studies. These limitations of liver biopsy have stimulated efforts to develop noninvasive approaches to stage NAFLD. As is true for many other types of chronic liver disease, in NAFLD the levels of serum aminotransferases (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]) do not reliably reflect the severity of liver cell injury, extent of liver cell death, or related liver inflammation and fibrosis. Thus, they are imperfect for determining which individuals with NAFLD have NASH. This has stimulated research to identify superior markers of liver injury. Serum levels of keratin 8 and keratin 18 appear to be promising surrogates. Keratins 8 and 18 (K8/18) are epithelial cytoskeletal proteins that undergo cleavage during programmed cell death (apoptosis). Both cleaved and full-length K8/18 are released into the blood as hepatocytes die, and studies suggest that serum levels of K8/18 differentiate individuals with NASH from those with simple steatosis or normal livers more reliably than do serum aminotransferase levels. Moreover, K8/18 levels appear to parallel the severity of liver fibrosis, with higher levels marking individuals who are likely to have worse scarring (i.e., advanced liver fibrosis or cirrhosis). While promising, testing for K8/18 has not yet become standard clinical practice. Other blood tests and imaging approaches that quantify liver fibrosis are also being developed. Recently, the U.S. Food and Drug Administration (FDA) approved an ultrasound-based test that measures liver stiffness as a surrogate marker of fibrosis (FibroScan®) **(Chap. 358)**. This new tool will likely be used serially to monitor fibrosis progression and regression in NAFLD patients. Studies that compare the receiver operator characteristics of K8/18 plus FibroScan® versus liver biopsy for monitoring NAFLD evolution are forthcoming.

CLINICAL FEATURES OF NAFLD

Most subjects with NAFLD are asymptomatic. The diagnosis is often made when abnormal liver aminotransferases or features of fatty liver are noted during an evaluation performed for other reasons. NAFLD may also be diagnosed during the workup of vague right upper quadrant abdominal pain, hepatomegaly, or an abnormal-appearing liver at time of abdominal surgery. Obesity is present in 50–90% of subjects. Most patients with NAFLD also have other features of the metabolic syndrome **(Chap. 422)**. Some have subtle stigmata of chronic liver disease, such as spider angiomata, palmer erythema, or splenomegaly. In a small minority of patients with advanced NAFLD, complications of end-stage liver disease (e.g., jaundice, features of portal hypertension such as ascites or variceal hemorrhage) may be the initial findings.

The association of NAFLD with obesity, diabetes, hypertriglyceridemia, hypertension, and cardiovascular disease is well known. Other associations include chronic fatigue, mood alterations, obstructive sleep apnea, thyroid dysfunction, and chronic pain syndrome. NAFLD is an independent risk factor for metabolic syndrome **(Chap. 422)**. Longitudinal studies suggest that patients with NASH are at two- to threefold increased risk for the development of metabolic syndrome. Similarly, studies have shown that patients with NASH have a higher risk for the development of hypertension and diabetes mellitus. The presence of NAFLD is also independently associated with endothelial dysfunction, increased carotid intimal thickness, and the number of plaques in carotid and coronary arteries. Such data indicate that NAFLD has many deleterious effects on health in general.

TREATMENT OF NAFLD

Treatment of NAFLD can be divided into three components: (1) specific therapy of NAFLD-related liver disease; (2) treatment of NAFLD-associated comorbidities; and (3) treatment of the complications of advanced NAFLD. The subsequent discussion focuses on specific therapies for NAFLD, with some mention of their impact on major NAFLD comorbidities (insulin resistance/diabetes, obesity, and dyslipidemia). Treatment of the complications of advanced NAFLD involves management of the complications of cirrhosis and portal hypertension, including primary liver cancers. Approaches to accomplish these objectives are similar to those used in other chronic liver diseases and are covered elsewhere in the textbook **(Chaps. 365 and 111)**.

At present, there are no FDA-approved therapies for the treatment of NAFLD. Thus, the current approach to NAFLD management focuses on treatment to improve the risk factors for NASH (i.e., obesity, insulin resistance, metabolic syndrome, dyslipidemia). Based on our understanding of the natural history of NAFLD, only patients with NASH or those with features of hepatic fibrosis on liver biopsy are considered currently for targeted pharmacologic therapies. This approach may change as our understanding of disease pathophysiology improves and potential targets of therapy evolve.

Diet and Exercise Lifestyle changes and dietary modification are the foundation for NAFLD treatment. Many studies indicate that lifestyle modification can improve serum aminotransferases and hepatic steatosis, with loss of at least 3–5% of body weight improving steatosis, but greater weight loss (up to 10%) necessary to improve steatohepatitis. The benefits of different dietary macronutrient contents (e.g., low-carbohydrate vs low-fat diets, saturated vs unsaturated fat diets) and different intensities of calorie restriction appear to be comparable. In adults with NAFLD, exercise regimens that improve fitness may be sufficient to reduce hepatic steatosis, but their impact on other aspects