

# Liver enzymes: No trivial elevations, even if asymptomatic

## ABSTRACT

Primary care physicians are at the forefront in screening for abnormal levels of liver enzymes and investigating the likely causes by obtaining a detailed history and physical examination, followed by appropriate laboratory and diagnostic workup. This review outlines common causes for the two main mechanisms of liver injury—cholestasis and hepatocellular insult—and explores the associated risk factors, methods of diagnosis, and management, with a focus on nonalcoholic fatty liver disease, one of the most often encountered causes of abnormal liver enzyme levels.

## KEY POINTS

Disorders of hepatocellular injury tend to elevate levels of aminotransferases, whereas cholestatic disorders cause elevations of alkaline phosphatase and bilirubin.

The three most common causes of liver enzyme elevation are alcohol toxicity, medication overdose, and fatty liver disease.

Other disorders of liver dysfunction include hereditary hemochromatosis, viral hepatitis, autoimmune hepatitis, primary biliary cholangitis, primary sclerosing cholangitis, and alpha-1 antitrypsin disease.

Nonhepatic causes of elevated “liver enzymes” also need to be considered. For instance, rhabdomyolysis causes elevations in aminotransferase levels.

ELEVATED LEVELS OF CIRCULATING enzymes that are frequently of hepatic origin (aminotransferases and alkaline phosphatase) and bilirubin in the absence of symptoms are common in clinical practice. A dogmatic but true statement holds that there are no trivial elevations in these substances. All persistent elevations of liver enzymes need a methodical evaluation and an appropriate working diagnosis.<sup>1</sup>

Here, we outline a framework for the workup and treatment of common causes of liver enzyme elevations.

### ■ PATTERN OF ELEVATION: CHOLESTATIC OR HEPATOCELLULAR

Based on the pattern of elevation, causes of elevated liver enzymes can be sorted into disorders of cholestasis and disorders of hepatocellular injury (Table 1).<sup>1</sup>

**Cholestatic disorders** tend to cause elevations in alkaline phosphatase, bilirubin, and gamma-glutamyl transferase (GGT).

**Hepatocellular injury** raises levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST).

### ■ HOW SHOULD ABNORMAL RESULTS BE EVALUATED?

When approaching liver enzyme elevations, the clinician should develop a working differential diagnosis based on the medical and social history and physical examination.

### Think about alcohol, drugs, and fat

The most common causes of liver enzyme elevation are alcohol toxicity, medication over-

dose, and fatty liver disease.

**Alcohol intake** should be ascertained. “Significant” consumption is defined as more than 21 drinks per week in men or more than 14 drinks per week in women, over a period of at least 2 years.<sup>2</sup>

The exact pathogenesis of alcoholic hepatitis is incompletely understood, but alcohol is primarily metabolized by the liver, and damage likely occurs during metabolism of the ingested alcohol. AST elevations tend to be higher than ALT elevations; the reason is ascribed to hepatic deficiency of pyridoxal 5'-phosphate, a cofactor of the enzymatic activity of ALT, which leads to a lesser increase in ALT than in AST.

Alcoholic liver disease can be difficult to diagnose, as many people are initially reluctant to fully disclose how much they drink, but it should be suspected when the ratio of AST to ALT is 2 or greater.

In a classic study, a ratio greater than 2 was found in 70% of patients with alcoholic hepatitis and cirrhosis, compared with 26% of patients with postnecrotic cirrhosis, 8% with chronic hepatitis, 4% with viral hepatitis, and none with obstructive jaundice.<sup>3</sup> Importantly, the disorder is often correctable if the patient is able to remain abstinent from alcohol over time.

**A detailed medication history** is important and should focus especially on recently added medications, dosage changes, medication overuse, and use of nonprescription drugs and herbal supplements. Common medications that affect liver enzyme levels include statins, which cause hepatic dysfunction primarily during the first 3 months of therapy, nonsteroidal anti-inflammatory drugs, anti-epileptic drugs, antibiotics, anabolic steroids, and acetaminophen (Table 2).<sup>1</sup> Use of illicit drugs and herbal remedies should be discussed, as they may cause toxin-mediated hepatitis.

Although inflammation from drug toxicity will resolve if the offending agent is discontinued, complete recovery may take weeks to months.<sup>4</sup>

**A pertinent social history** includes exposure to environmental hepatotoxins such as amatoxin (contained in some wild mushrooms) and occupational hazards (eg, vinyl chloride). Risk factors for viral hepatitis should be evaluated, including intravenous drug use,

TABLE 1

**Liver disease and associated liver enzyme elevations**

**Hepatocellular disease**

(aminotransferase elevations predominate)

Common

- Alcoholic liver disease
- Autoimmune hepatitis
- Chronic viral hepatitis
- Genetic hemochromatosis (northern European ethnicity)
- Medication toxicity (see Table 2)
- Nonalcoholic fatty liver disease

Less common

- Alpha-1 antitrypsin deficiency
- Wilson disease

**Cholestatic disease**

(alkaline phosphatase, bilirubin, and gamma-glutamyl transferase elevations predominate)

Common

- Biliary obstruction (eg, gallstones)
- Drug hepatotoxicity
- Neoplasm
- Primary biliary cirrhosis
- Primary sclerosing cholangitis

Less common

- Autoimmune cholangiopathy
- Sarcoidosis

From Aragon G, Zounossi ZM. When and how to evaluate mildly elevated liver enzymes in apparently healthy patients. *Cleve Clin J Med* 2010; 77(3):195–204. doi:10.3949/ccjm.77a.09064.

blood transfusions, unprotected sexual contact, organ transplant, perinatal transmission, and a history of work in healthcare facilities or travel to regions in which hepatitis A or E is endemic.

**The medical and family history** should include details of associated conditions, such as:

- Right heart failure (a cause of congestive hepatopathy)
- Metabolic syndrome (associated with fatty liver disease)
- Inflammatory bowel disease and primary sclerosing cholangitis
- Early-onset emphysema and alpha-1 antitrypsin deficiency.

**The physical examination** should be thor-

**‘Significant’ alcohol consumption is > 21 drinks per week in men, and > 14 drinks per week in women, for ≥ 2 years**

TABLE 2

**Hepatotoxicity of selected drugs**

**Hepatocellular abnormalities**

- Acetaminophen—acute hepatitis
- Allopurinol—granuloma
- Azathioprine—veno-occlusive disease, nodular regenerative hyperplasia
- Chaparral—portal inflammation with bile duct proliferation, lobar necrosis, and collapse
- Diclofenac, other nonsteroidal anti-inflammatory drugs
- Hydralazine—granuloma
- Isoniazid
- Methotrexate—fibrosis
- Methyldopa
- Mistletoe—hepatocellular injury
- Nitrofurantoin—autoimmune-like disease
- Quinidine—granuloma
- Statins
- Toxic alkaloid—veno-occlusive disease

**Cholestatic abnormalities**

- Amoxicillin-clavulanate, other penicillin derivatives
- Anabolic steroids—cholestasis, peliosis hepatis, neoplasm
- Captopril
- Carbamazepine
- Chlorpromazine
- Erythromycin estolate
- Estrogens
- Kava—hepatic necrosis, cholestasis, lobular hepatitis
- Oral contraceptives
- Phenytoin—mononucleosis-like syndrome
- Sulfa drugs

**Drug-induced fatty liver**

- (with or without hepatocellular abnormalities)
- Amiodarone —phospholipidosis
- Anabolic steroids—cholestasis, peliosis hepatis, neoplasm
- Cocaine—microvesicular steatosis
- Corticosteroids
- Jin Bu Huan—focal hepatic necrosis, steatosis, bridging fibrosis
- Tetracycline
- Valproic acid

Adapted from Aragon G, Zounossi ZM. When and how to evaluate mildly elevated liver enzymes in apparently healthy patients. *Cleve Clin J Med* 2010; 77(3):195–204. doi:10.3949/ccjm.77a.09064.

Up to 1/3 of the US population—100 million people—may have NAFLD, and 4–6 million may have NASH

ough, with emphasis on the abdomen, and search for stigmata of advanced liver disease such as hepatomegaly, splenomegaly, ascites, edema, spider angiomas, jaundice, and asterix. Any patient with evidence of chronic

liver disease should be referred to a subspecialist for further evaluation.

**Further diagnostic workup**

Abnormal liver enzyme findings or physical examination findings should direct the subsequent diagnostic workup with laboratory testing and imaging.<sup>5</sup>

**For cholestasis.** If laboratory data are consistent with cholestasis or abnormal bile flow, it should be further characterized as extrahepatic or intrahepatic. Common causes of extrahepatic cholestasis include biliary tree obstruction due to stones or malignancy, often visualized as intraductal biliary dilation on ultrasonography of the right upper quadrant. Common causes of intrahepatic cholestasis include viral and alcoholic hepatitis, nonalcoholic steatohepatitis, certain drugs and toxins such as alkylated steroids and herbal medications, infiltrative diseases such as amyloid, sarcoid, lymphoma, and tuberculosis, and primary biliary cholangitis.

Abnormal findings on ultrasonography should be further pursued with advanced imaging, ie, computed tomography or magnetic resonance cholangiopancreatography (MRCP). The confirmation of a lesion on imaging is often followed by endoscopic retrograde cholangiopancreatography (ERCP) in an attempt to obtain biopsy samples, remove obstructions, and place therapeutic stents. In instances when endoscopic attempts fail to relieve the obstruction, surgical referral may be appropriate.

**For nonhepatobiliary problems.** Depending on clinical presentation, it may also be important to consider nonhepatobiliary causes of elevated liver enzymes.

Alkaline phosphatase is found in many other tissue types, including bone, kidney, and the placenta, and can be elevated during pregnancy, adolescence, and even after fatty meals due to intestinal release.<sup>6</sup> After screening for the aforementioned physiologic conditions, isolated elevated alkaline phosphatase should be further evaluated by obtaining GGT or 5-nucleotidase levels, which are more specifically of hepatic origin. If these levels are within normal limits, further evaluation for conditions of bone growth and cellular turnover such as Paget disease, hyperparathyroidism,

and malignancy should be considered. Specifically, Stauffer syndrome should be considered when there is a paraneoplastic rise in the alkaline phosphatase level in the setting of renal cell carcinoma without liver metastases.

AST and ALT levels may also be elevated in clinical situations and syndromes unrelated to liver disease. Rhabdomyolysis, for instance, may be associated with elevations of AST in more than 90% of cases, and ALT in more than 75%.<sup>7</sup> Markers of muscle injury including serum creatine kinase should be obtained in the setting of heat stroke, muscle weakness, strenuous activity, or seizures, as related elevations in AST and ALT may not always be clinically indicative of liver injury.

Given the many conditions that may cause elevated liver enzymes, evaluation and treatment should focus on identifying and removing offending agents and targeting the underlying process with appropriate medical therapy.

## ■ FATTY LIVER

With rates of obesity and type 2 diabetes on the rise in the general population, identifying and treating nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) require increased awareness and close coordination between primary care providers and subspecialists.

According to current estimates, up to one-third of the US population (100 million people) may have NAFLD, and 1% to 3% of the population (4–6 million people) likely have NASH, defined as steatosis with inflammation. Development of NASH places patients at a significantly higher risk of fibrosis, hepatocellular injury, and cancer.<sup>8</sup>

NAFLD is more common in men than in women. It is present in around 80% to 90% of obese adults, two-thirds of adults with type 2 diabetes, and many people with hyperlipidemia. It is also becoming more common in children, with 40% to 70% of obese children likely having some element of NAFLD.

### Diagnosis of fatty liver

Although liver enzymes are more likely to be abnormal in individuals with NAFLD, many individuals with underlying NAFLD may have normal laboratory evaluations. ALT may be elevated in only up to 20% of cases and

does not likely correlate with the level of underlying liver damage, although increasing GGT may serve as a marker of fibrosis over time.<sup>9–11</sup> In contrast to alcohol injury, however, the AST-ALT ratio is usually less than 1.0.

Noninvasive tools for diagnosing NAFLD include the NAFLD fibrosis score, which incorporates age, hyperglycemia, body mass index, platelet count, albumin level, and AST-ALT ratio. This and related scoring algorithms may be useful in differentiating patients with minimal fibrosis from those with advanced fibrosis.<sup>12,13</sup>

Ultrasonography is a first-line diagnostic test for steatosis, although it may demonstrate fatty infiltration only around 60% of the time. Computed tomography and magnetic resonance imaging are more sensitive, but costlier. Transient elastography (FibroScan; Echosens, Paris, France) has become more popular and has been shown to correlate with findings on liver biopsy in diagnosing or excluding advanced liver fibrosis.<sup>14,15</sup>

The gold standard for diagnosing NAFLD and NASH is identifying fat-laden hepatocytes or portal inflammation on biopsy; however, biopsy is generally reserved for cases in which the diagnosis remains uncertain.

### Behavioral treatment

The primary treatment for NAFLD consists of behavioral modification including weight loss, exercise, and adherence to a low-fat diet, in addition to tight glycemic control and treatment of any underlying lipid abnormalities. Studies have shown that a reduction of 7% to 10% of body weight is associated with a decrease in the inflammation of NAFLD, though no strict guidelines have been established.<sup>16</sup>

Given the prevalence of NAFLD and the need for longitudinal treatment, primary care physicians will play a significant role in long-term monitoring and management of patients with fatty liver disease.

## ■ OTHER DISORDERS OF LIVER FUNCTION

### Hereditary hemochromatosis

Hereditary hemochromatosis is the most common inherited liver disorder in adults of European descent,<sup>17</sup> and can be effectively treated if discovered early. But its clinical diagnosis can be challenging, as many patients have no

**Treatment for NAFLD: weight loss, exercise, low-fat diet, tight glycemic control, lipid control**

symptoms at presentation despite abnormal liver enzyme levels. Early symptoms may include severe fatigue, arthralgias, and, in men, impotence, before the appearance of the classic triad of “bronze diabetes” with cirrhosis, diabetes, and darkening of the skin.<sup>18</sup>

If hemochromatosis is suspected, laboratory tests should include a calculation of percent transferrin saturation, with saturation greater than 45% warranting serum ferritin measurement to evaluate for iron overload (ferritin > 200–300 ng/mL in men, > 150–200 ng/mL in women).<sup>19</sup> If iron overload is confirmed, referral to a gastroenterologist is recommended.

Genetic evaluation is often pursued, but patients may ultimately require liver biopsy regardless of the findings, as some patients homozygous for the *HFE* mutation C282Y may not have clinical hemochromatosis, whereas others with hereditary hemochromatosis may not have the *HFE* mutation.

Therapeutic phlebotomy is the treatment of choice, and most patients tolerate it well.

### Chronic hepatitis B virus and hepatitis C virus infections

Chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections are common in the United States, with HBV affecting more than 1 million people and HCV affecting an estimated 3.5 million.

**Chronic HCV infection.** Direct-acting antiviral drugs have revolutionized HCV treatment and have led to a sustained viral response and presumed cure at 12 weeks in more than 95% of cases across all HCV genotypes.<sup>20</sup> Given the recent development of effective and well-tolerated treatments, primary care physicians have assumed a pivotal role in screening for HCV.

The American Association for the Study of Liver Diseases and the Infectious Diseases Society of America<sup>21</sup> recommend screening for HCV in people who have risk factors for it, ie:

- HCV exposure
- HIV infection
- Behavioral or environmental risks for contracting the virus such as intravenous drug use or incarceration
- Birth between 1945 and 1965 (one-time testing).

If HCV antibody screening is positive,

HCV RNA should be obtained to quantify the viral load and confirm active infection, and genotype testing should be performed to guide treatment. Among the 6 most common HCV genotypes, genotype 1 is the most common in North America, accounting for over 70% of cases in the United States.

Although recommendations and therapies are constantly evolving, the selection of a treatment regimen and the duration of therapy are determined by viral genotype, history of prior treatment, stage of liver fibrosis, potential drug interactions, and frequently, medication cost and insurance coverage.

**HBV infection.** The treatment for acute HBV infection is generally supportive, though viral suppression with tenofovir or entecavir may be required for those who develop coagulopathy, bilirubinemia, or liver failure. Treatment of chronic HBV infection may not be required and is generally considered for those with elevated ALT, high viral load, or evidence of liver fibrosis on noninvasive measurements such as transient elastography.

### Autoimmune hepatitis

Autoimmune causes of liver enzyme elevations should also be considered during initial screening. Positive antinuclear antibody and positive antismooth muscle antibody tests are common in cases of autoimmune hepatitis.<sup>22</sup> Autoimmune hepatitis affects women more often than men, with a ratio of 4:1. The peaks of incidence occur during adolescence and between ages 30 and 45.<sup>23</sup>

### Primary biliary cholangitis

Additionally, an elevated alkaline phosphatase level should raise concern for underlying primary biliary cholangitis (formerly called primary biliary cirrhosis), an autoimmune disorder that affects the small and medium intrahepatic bile ducts. Diagnosis of primary biliary cholangitis can be assisted by a positive test for antimitochondrial antibody, present in almost 90% of patients.<sup>24</sup>

### Primary sclerosing cholangitis

Elevated alkaline phosphatase is also the hallmark of primary sclerosing cholangitis, which is associated with inflammatory bowel disease.<sup>25</sup> Primary sclerosing cholangitis is

**Screen for HCV in those with HCV exposure, HIV infection, IV drug use, incarceration, or in those born 1945 to 1965 (one-time testing)**

characterized by inflammation and fibrosis of the intrahepatic and extrahepatic bile ducts, which are visualized on MRCP and confirmed by biopsy if needed.

REFERRAL

Subspecialty referral should be considered if the cause remains ambiguous or unknown, if

there is concern for a rare hepatic disorder such as an autoimmune condition, Wilson disease, or alpha-1 antitrypsin deficiency, or if there is evidence of advanced or chronic liver disease.

Primary care physicians are at the forefront of detecting and diagnosing liver disease, and close coordination with subspecialists will remain crucial in delivering patient care.

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ADDRESS: Brian Agganis, MD, Department of Internal Medicine, Brown University, 593 Eddy Street, Jane Brown Ground, Suite 0100, Providence, RI 02903; brian.agganis@lifespan.org

## Liver enzymes

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In the article by Agganis B, Lee D, Sepe T (Liver enzymes: No trivial elevations, even if asymptomatic. *Cleve Clin J Med* 2018; 85(8):612–617, doi:10.3949/ccjm.85a.17103), an error occurred on page 613, in the second paragraph in the section about alcohol intake. The words ALT and AST were reversed. The paragraph should read as follows:

*The exact pathogenesis of alcoholic hepatitis is*

*incompletely understood, but alcohol is primarily metabolized by the liver, and damage likely occurs during metabolism of the ingested alcohol. AST elevations tend to be higher than ALT elevations; the reason is ascribed to hepatic deficiency of pyridoxal 5'-phosphate, a cofactor of the enzymatic activity of ALT, which leads to a lesser increase in ALT than in AST.*

We thank Avinash Alexander, MD, Texas Tech University Health Sciences Center, for calling this to our attention. The correction has been made online.