REVIEW

ZOBAIR M. YOUNOSSI, MD, MPH
Associate Staff Physician, Department of Gastroenterology, Cleveland Clinic.

Evaluating asymptomatic patients with mildly elevated liver enzymes

ABSTRACT

Because elevated liver enzymes are found in 1% to 4% of asymptomatic persons, extensive evaluation of all abnormal tests would expose many patients to undue risks and medical costs. On the other hand, not evaluating minor elevations of liver enzymes could result in missing the early diagnosis of potentially treatable disorders. This review discusses likely causes of elevated aminotransferase, alkaline phosphatase, and gamma-glutamyl transferase levels and provides algorithms for evaluating abnormal liver enzyme values in apparently healthy patients in the primary care setting.

KEY POINTS

Hepatitis C virus is the most common cause of chronic liver disease and cirrhosis, and the main indication for liver transplantation in the United States.

Suspect alcoholic liver disease when a patient exhibits addictive behavior and when the aspartate and alanine aminotransferase levels are elevated, with the aspartate aminotransferase level higher.

If medication or alcohol is a suspected cause of elevated aminotransferase levels, retest the levels after 6 to 8 weeks of abstinence.

IN SEEMINGLY HEALTHY PATIENTS, abnormal liver enzymes levels challenge even experienced clinicians in deciding what further evaluation to pursue. Over the past decade, automated laboratory testing has made serum liver enzyme levels easy to obtain, and consequently, testing has increased—and so have incidental abnormal findings. An estimated 1% to 4% of asymptomatic people have abnormal liver enzyme levels when screened using standard biochemistry panels.[1]

These findings can lead to extensive evaluations that can be costly, anxiety-provoking, and risky, especially if they lead to unnecessary invasive procedures such as a liver biopsy or endoscopic retrograde cholangiopancreatography.

Not all asymptomatic persons with a single, isolated mild elevation in a liver enzyme have underlying liver disease or require extensive evaluation. Factors to consider in evaluating these patients include:

- The patient's overall health.
- The prevalence of different liver disorders in the community.
- The duration and pattern of enzyme elevation.
- Whether therapy is available.
- The costs and risks associated with additional evaluation.

This review discusses the most likely causes of elevated aminotransferase, alkaline phosphatase, and gamma-glutamyl transferase levels. It also provides algorithms primary care providers can use to evaluate abnormal liver enzyme values in apparently healthy patients.

PATTERNS OF LIVER ENZYME ELEVATION

Although the term "liver function test" is commonly used to describe liver enzyme evaluations, the term should be reserved for biochemical tests that assess the functional hepatic reserve—traditionally, the albumin level and the prothrombin time.[2] On the other hand, elevated serum liver enzymes (aminotransferases, alkaline phosphatase, and gamma-glutamyl transferase) can reflect abnormalities in either liver cells or the bile duct. The enzyme that is most elevated suggests different types of liver disease.

Aminotransferase elevation suggests hepatocellular damage. Normal serum levels are < 40 U/L for aspartate aminotransferase (AST) and < 50 U/L for alanine aminotransferase (ALT).

Alkaline phosphatase elevation (adult normal serum levels between 20 and 120 U/L) suggests biliary obstruction, injury to the bile duct epithelium, and cholestasis.

Gamma-glutamyl transferase elevation (normal range 0 to 50 U/L in men, 0 to 35 U/L in women) is a marker of either type of disease, but the most sensitive marker of biliary tract disease.

TABLE 1

Liver diseases: Frequency of occurrence

Hepatocellular diseases (aminotransferase elevations predominate)

Common
- Chronic viral hepatitis
- Genetic hemochromatosis (northern European descent)
- Alcoholic liver disease
- Nonalcoholic steatohepatitis
- Medication toxicity (see TABLE 2)
- Autoimmune hepatitis

Less common
- Wilson's disease
- Alpha-1-antitrypsin deficiency

Cholestatic diseases (alkaline phosphatase and gamma-glutamyl transferase elevations predominate)

Common
- Primary biliary cirrhosis
- Primary sclerosing cholangitis
- Neoplasms
- Biliary obstruction (gallstones, etc)
- Drug hepatotoxicity

Less common
- Autoimmune cholangiopathy
- Sarcoidosis

PREVALENCE OF LIVER DISEASES AND EVALUATION OF ELEVATED SERUM ENZYMES

Before starting an extensive evaluation of a patient with an elevated liver enzyme, one should consider the prevalence and the predisposing risks for different liver disorders (TABLE 1). These epidemiologic data, plus other clinical data obtained from the history and physical examination, provide important clues to guide further investigation.

Chronic viral hepatitis

Prevalence. Hepatitis C virus (HCV) infection affects an estimated 1.8% of the general population, and 14.4% of persons with ALT levels greater than 40 U/L, making it the most common cause of chronic liver disease, cirrhosis, and liver transplantation in the United States. Hepatitis B virus (HBV) infection is somewhat less common: between 0.2% and 0.9% of the general population have positive reactions to HBV surface antigen. The prevalence of both viruses increases dramatically in the presence of risk factors (see below).

Risk factors. Risk factors include blood product transfusion, intravenous drug use, hemodialysis, and birth in an endemic region. Although both viruses can be transmitted sexually, HBV is more readily transmitted in this way than HCV. It should be noted that 30% to 40% of people infected with these viruses have no identifiable risk factors.

Comments. Most patients with chronic viral hepatitis have no symptoms or only mild symptoms and minimally elevated aminotransferase levels (two to five times higher than the upper limit of normal). Given the relatively high prevalence of HCV, serologic testing for HCV should be done early in the course of evaluating a patient with chronically elevated liver enzyme levels.[3,4]

The most common chronic liver disease in the United States is chronic viral hepatitis

TABLE 2

Medications with potential for hepatotoxicity

Hepatocellular abnormalities

- Allopurinol (granuloma)
- Azathioprine (veno-occlusive disease)
- Diclofenac and other nonsteroidal anti-inflammatory drugs
- Hydralazine (granuloma)
- Isoniazid
- Methotrexate (fibrosis)
- Methyldopa
- Nitrofurantoin (autoimmune-like)
- Quinidine (granuloma)

Cholestatic abnormalities

- Amoxicillin-clavulanate and other penicillin derivatives
- Anabolic steroids
- Captopril
- Chlorpromazine
- Erythromycin estolate
- Estrogens
- Oral contraceptive
- Phenytoin (mononucleosis-like syndrome)
- Sulfa drugs

Fatty liver (with or without hepatocellular abnormalities)

- Amiodarone (phospholipidosis)
- Corticosteroids
- Tetracycline
- Valproic acid

Genetic hemochromatosis

Prevalence. The prevalence is 0.25% to 0.5% for people of northern European descent, of whom 1 in 10 is heterozygous and 1 in 200 to 400 is homozygous for the mutated gene.

Risk factors. Northern European ancestry is the primary risk factor. In men, the onset of disease is usually in the third and fourth decades of life, while menses protects women until menopause. Recently, mutations in a gene related to the major histocompatibility complex class I family (termed HFE) have been shown to be present in 83% to 85% of people homozygous for genetic hemochromatosis. Although this test is currently considered a research tool, it may become very useful in screening for and diagnosing this condition.

Comments. Genetic hemochromatosis should be considered early in the evaluation of male patients of northern European descent. Patients usually have no symptoms until iron overload causes significant end-organ damage. Phlebotomy is an extremely effective treatment for this potentially fatal disease.[5]

Alcoholic liver disease

Prevalence. The prevalence varies, depending on a variety of factors, including volume and duration of alcohol ingestion, type of liver disease, genetics, and coexistence of viral hepatitis.

Risk factors. Alcohol-related liver disease can range from simple fatty liver to alcoholic hepatitis with or without cirrhosis. Cirrhosis develops in only 20% to 30% of patients who consume a substantial amount of alcohol, defined as more than a decade of 60 to 80 g/day of alcohol in men and as little as 20 to 40 g/day in women. (A standard drink contains 12 g of alcohol, equal to one 12-ounce beer, a 5-ounce glass of wine, or 1.5 ounces of distilled spirits.) Female gender, chronic viral hepatitis (especially HCV), genetic hemochromatosis, and certain medications (eg, methotrexate) potentiate the harmful effects of alcohol.

Comments. Although cirrhosis affects less than a third of such long-term heavy drinkers, early detection and treatment can potentially reduce morbidity and early mortality. Alcoholic liver disease should be suspected in people whose behavior suggests an addictive personality and in those with elevated ALT and AST levels in whom the AST level is higher.[6]

Nonalcoholic steatohepatitis (fatty liver)

Prevalence. The prevalence is not well defined, but populations at risk, such as patients with type 2 (formerly "adult-onset") diabetes, can have prevalence rates as high as 50%. It is perhaps the most common cause of mildly elevated liver enzymes in the United States.

Risk factors. Obesity, diabetes, hyperlipidemia, medications (TABLE 2), and jejunoileal bypass surgery are the major risk factors.

Comments. Nonalcoholic steatohepatitis and steatonecrosis are terms recently coined to describe a form of fatty liver disease with a

potentially progressive course. Although these disorders are histologically indistinguishable from alcohol-induced liver disease, their mechanism is not well understood: theories include abnormalities of lipid metabolism with increased hepatic lipid peroxidation, activated fibrocytes, and abnormal patterns of cytokine production. Data from a few limited natural history studies suggest that simple steatosis has a benign course, while nonalcoholic steatohepatitis or steatonecrosis can progress to cirrhosis in 10% to 20% of patients.[7] Treatment of obesity, hyperlipidemia, and diabetes may have limited benefit but should be undertaken.

Autoimmune hepatitis

Prevalence. The prevalence of autoimmune hepatitis depends on the geographic location and the extent of viral hepatitis in the community. In Hong Kong, only 1% of all cases of chronic hepatitis are secondary to autoimmune hepatitis. By contrast, 34% and 62% of patients with chronic hepatitis in Germany and Australia may have autoimmune hepatitis.[9] In North America, the prevalence of autoimmune hepatitis among patients with chronic liver disease is estimated to be 11% to 23%. The incidence of autoimmune hepatitis is about 0.69 per 100,000 individuals each year in North America. In addition to underlying genetic differences, selection bias can explain the variability seen in these prevalence rates.

Risk factors. Autoimmune hepatitis is predominantly seen in women.

Comments. The diagnosis of autoimmune hepatitis is suspected by excluding viral causes of chronic hepatitis and by the presence of autoimmune markers such as antinuclear antibody, smooth muscle antibody, and liver-kidney microsomal antibody. Treatment with immunosuppression is effective, and this diagnosis should be considered in all individuals (especially in female patients) with chronic elevation of liver enzymes.

Primary biliary cirrhosis

Prevalence. In one study of urban-dwelling women in northeast England, the prevalence of primary biliary cirrhosis was estimated at 0.10%.[8]

Risk factors. Like autoimmune hepatitis, primary biliary cirrhosis is predominantly seen in women.

Comments. Treatment of primary biliary cirrhosis with ursodeoxycholic acid improves liver enzyme levels, may lead to histological improvement and increased survival, and may also delay the need for liver transplantation.[8,9]

Wilson's disease

Prevalence. The prevalence is estimated at 1 in 30,000 in most populations.

Risk factors. Any person younger than age 40 with abnormal liver enzyme levels should be evaluated for Wilson's disease, even in the absence of neurologic or ocular findings. However, such routine screening is rarely fruitful in persons older than age 50.

Comments. Effective therapy is available (eg, D-penicillamine, trientine, zinc). For Wilson's disease, alpha-1-antitrypsin deficiency, and genetic hemochromatosis, establishing the diagnosis is not only important to the individual patient, but may also be important in screening the asymptomatic members of the proband's family.[10,11]

Alpha-1-antitrypsin deficiency

Prevalence. Alpha-1-antitrypsin deficiency occurs in 1 of every 1,600 to 1,800 live births.

Risk factors. A patient with emphysema or who has a young sibling with liver failure should undergo an investigation for alpha-1-antitrypsin deficiency, consisting of a measurement of the alpha-1-antitrypsin level and a genetic study to look for phenotype PiZZ.

Comments. Liver transplantation is the only effective therapy available for the treatment of liver disease associated with alpha-1-antitrypsin deficiency.

Medication-related and toxin-related liver diseases

NSAIDs and penicillin-derived antibiotics can cause abnormal liver enzyme levels

Nonsteroidal anti-inflammatory drugs (NSAIDs) and penicillin-derived antibiotics are the drugs that most commonly cause abnormal serum liver enzyme levels. The mechanism of drug-induced liver disease ranges from induction of hepatic enzymes (caused by anticonvulsants) to allergic reaction, autoimmunity (nitrofurantoin), idiosyn-

cratic reaction, and veno-occlusive injury. Some medications with potential for hepatotoxicity are listed in TABLE 2.

A variety of environmental agents can injure the liver, including vinyl chloride (fibrosis, portal hypertension, angiosarcoma), carbon tetrachloride (acute hepatocyte necrosis), aflatoxin, and *Amanita* types of mushrooms (hepatocyte necrosis).

Given the availability of over-the-counter and prescribed medications and the potential for exposure to toxins, a thorough history of exposure to such agents is crucial.[12]

MILD ENZYME ELEVATIONS AS INDICATORS OF SPECIFIC DISEASES

Despite the potential importance—and the frequency—of discovering an abnormal liver enzyme level, very few well-designed prospective studies have addressed this issue. Most of the information presented here comes from small retrospective studies that lack accurate information on the important causes of liver disease such as HCV infection and nonalcoholic steatohepatitis. Despite these shortcomings, the literature delineates three patterns of mild liver enzyme elevations, depending on which enzyme is predominantly elevated: aminotransferase, alkaline phosphatase, or gamma-glutamyl transferase.

An AST level more than twice that of the ALT suggests alcohol-induced liver damage

Aminotransferase elevation

Causes of aminotransferase elevation. Aminotransferases are commonly used markers of hepatocyte injury. AST is found in blood cells and many tissues, including liver, muscle, brain, pancreas, and lung. ALT is a cytosolic enzyme found primarily in hepatocytes, making it a more specific indicator of liver disease.

Acute viral hepatitis, toxins, and liver ischemia can markedly elevate serum aminotransferase levels (into the thousands). On the other hand, these enzymes are mildly elevated (< 300 U/L) in nonalcoholic steatohepatitis, chronic hepatitis, cholestatic liver conditions, drug-induced hepatotoxicity, and liver tumors. Because AST is a mitochondrial enzyme and is affected by alcohol ingestion, an AST level more than twice that of the ALT suggests hepatic damage due to alcohol. Of note, aminotransferase elevation can also be due to nonhepatic causes; for example, muscle necrosis can result in mild elevation of these enzymes, especially AST.

Only a few studies have documented the results of a thorough evaluation of patients with mildly elevated aminotransferase levels. Hultcrantz[1] studied 149 consecutive patients with chronic, asymptomatic, mild elevations of AST or ALT who underwent a full evaluation, including liver biopsy. Of these patients, 63% had "fatty liver," 20% had "chronic hepatitis," and 17% had miscellaneous diagnoses. Whether patients in the "chronic hepatitis" group had HCV was not determined because serologic testing was not available at the time.

Friedman et al[13] studied 100 healthy blood donors with an elevated ALT level and found that in 33% of patients the elevation occurred once, in 36% it was intermittent, and in 28% it was persistent. In this series, 45% of patients had no diagnosis, 22% were obese (presumed to have nonalcoholic steatohepatitis), 5% had alcoholic liver disease, 3% had "resolving hepatitis," 1% had hemochromatosis, and 1% had "cytomegalovirus hepatitis." Although these patients underwent a complete history, physical, and serologic testing, liver biopsies were not done to confirm the clinical diagnosis.

Hay et al[14] described 47 patients with chronically elevated aminotransferases (threefold to eightfold) who underwent full evaluation and liver biopsy and who had no clinical symptoms of alcoholic, viral, or drug-induced liver disease. A diagnosis of steatohepatitis was given in 10 patients, another 34 were diagnosed with "chronic hepatitis," and 3 had miscellaneous diagnoses. Of patients with chronic hepatitis, 16 had evidence of cirrhosis on biopsy, and 18 tested positive for at least one autoimmune marker (antinuclear antibody or smooth muscle antibody).

The above studies suggest that fatty liver caused by either alcohol or nonalcoholic steatohepatitis is the major cause of mildly elevated aminotransferases. Chronic hepatitis is the other common diagnosis associated with mild elevation of aminotransferases. Two major drawbacks of these studies include lack of data on HCV serology in patients with the

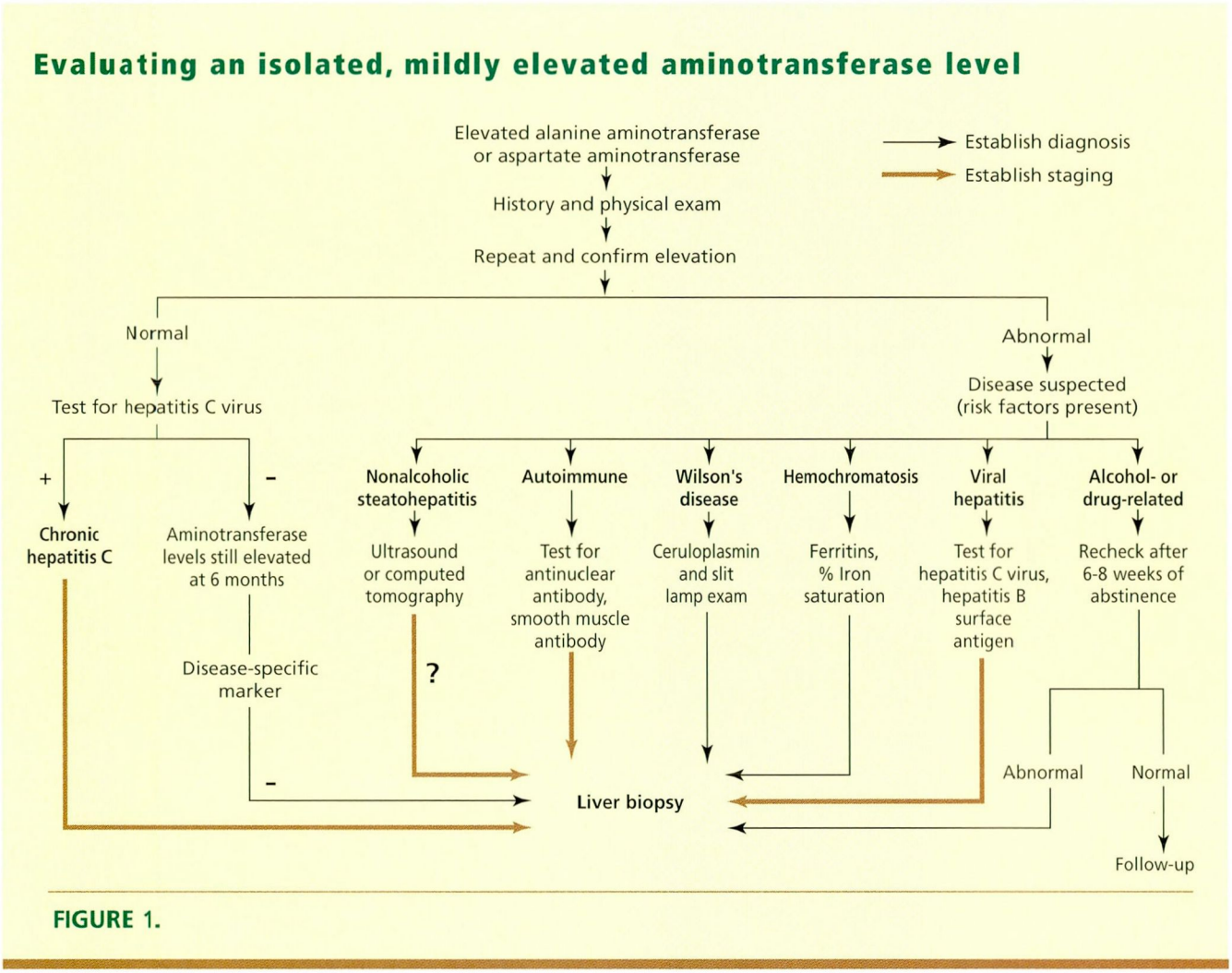

FIGURE 1.

diagnosis of "chronic hepatitis" and a lack of uniform approach to the pathologic diagnosis of nonalcoholic steatohepatitis. With serologic testing for HCV now widely available, it is possible that a substantial portion of persons with "chronic hepatitis" can further be classified as having chronic hepatitis C.

Clinical workup. FIGURE 1 shows an algorithm for evaluating patients with elevated aminotransferase levels on an initial examination. The first step is to confirm the abnormality by repeating the blood test. If an enzyme elevation is confirmed, further investigation is warranted.

A directed history and physical examination can give crucial clues in the preliminary workup. The history may disclose risk factors for:

- Viral hepatitis (intravenous drug use, natives of endemic areas of the world, blood product transfusions, etc).
- Alcoholic liver disease.
- Medication exposure.
- Genetic liver disorders (family history of liver disease).
- Possible coexisting diseases (diabetes and obesity in nonalcoholic steatohepatitis, neurologic disorders in Wilson's disease, emphysema in alpha-1-antitrypsin deficiency, thyroid disease in autoimmune hepatitis and primary biliary cirrhosis, and diabetes and impotence in genetic hemochromatosis).

Although the physical signs of chronic liver disease (eg, spider angiomata, palmar erythema, gynecomastia) are nonspecific, some physical findings (eg, Kayser-Fleischer rings

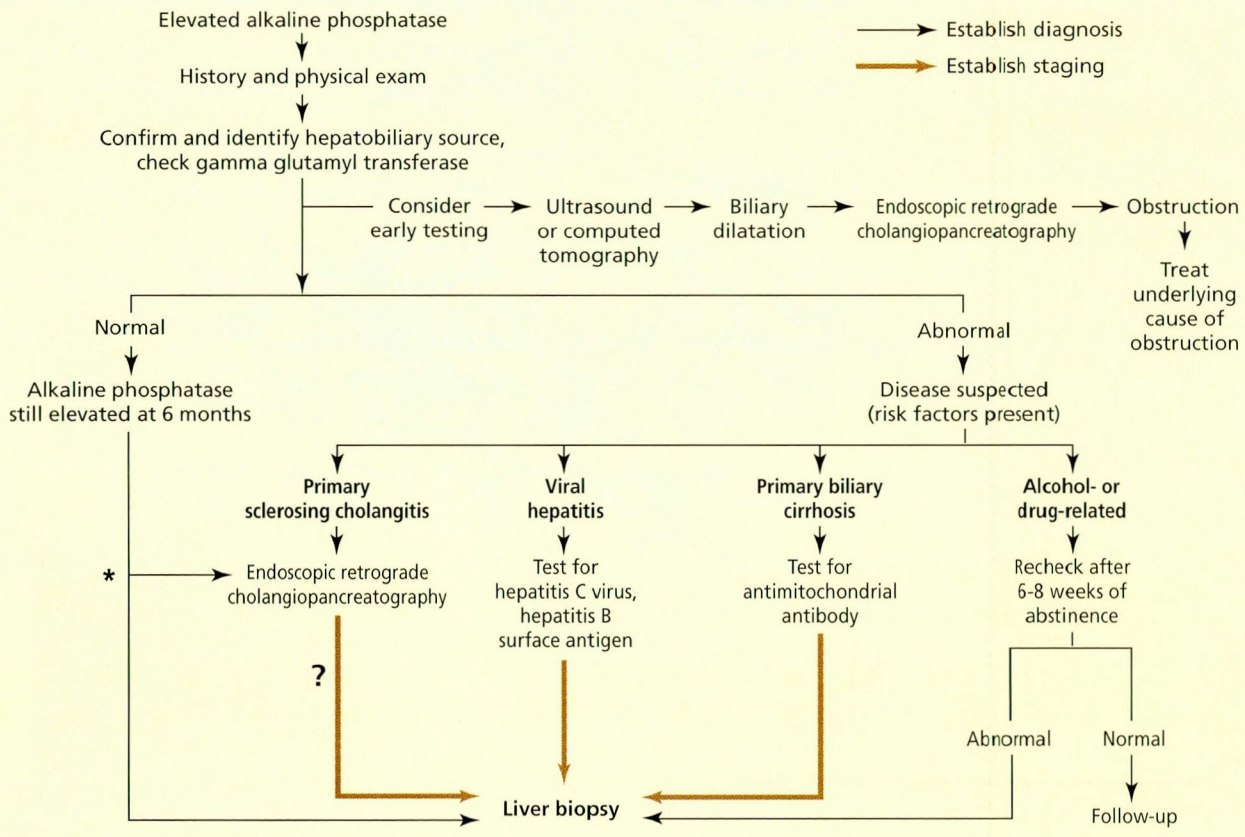

FIGURE 2. *The decision is based on clinical suspicion for biliary disease vs cholestatic disease

on slit lamp examination for Wilson's disease, hypertrophy of the second and third metacarpophalangeal joint for hemochromatosis) suggest potential causes. Iron studies for middle-aged men, autoimmune markers for women, and screening for Wilson's disease in young patients are helpful when the clinical information points to one of these entities as a potential diagnosis.

If medication or alcohol is a suspected cause, aminotransferase levels should be repeated after 6 to 8 weeks of abstinence. If nonalcoholic steatohepatitis is suspected, we recommend repeating tests after treating the potential risk factor (obesity, diabetes, hyperlipidemia) for 8 to 12 weeks. An imaging study (ultrasound or computed tomography scan) may show increased hepatic echogenicity, suggesting increased fatty infiltration, in addition to excluding most hepatic tumors.

If the clinical data obtained from the history and physical examination raise clinical suspicion for a particular disease, a disease-specific marker (FIGURES 1 AND 2) can further help in supporting the potential diagnosis. Remember: liver biopsy remains the gold standard in establishing the diagnosis for most liver disorders and is the only method currently available to establish cirrhosis with important prognostic implications.[15]

If the history and physical do not suggest any particular condition, serologic testing for HCV should be obtained. If negative, other selected testing can be helpful (iron studies in a male patient, autoimmune markers in women, ceruloplasmin and slit lamp examina-

tion in a young individual). If the preliminary workup remains negative and the aminotransferase levels remain elevated for 6 months, a liver biopsy is indicated to establish the diagnosis. Features in the liver biopsy specimens may provide further confirmation of the diagnosis: eg, periodic acid-Schiff-positive globules in alpha-1-antitrypsin deficiency, hepatic iron index for hemochromatosis, and hepatic copper content for Wilson's disease.

Alkaline phosphatase elevation

Causes of alkaline phosphatase elevation. Alkaline phosphatase activity has been found in multiple organs, including the liver, bones, small bowel, kidneys, and placenta. Diseases of the hepatobiliary system can result in moderately to markedly elevated alkaline phosphatase levels. Any conditions associated with bone involvement, such as Paget's disease, sarcoma, metastatic disease, hyperparathyroidism, and rickets, can elevate the alkaline phosphatase level. Elevated gamma-glutamyl transferase in conjunction with elevated alkaline phosphatase usually points to a hepatobiliary source. Now rarely done, isoenzyme fractionation of alkaline phosphatase may help further distinguish the source of the elevation and identify the liver, bone, or other organ as the predominant origin of this abnormality.

Hepatobiliary causes of alkaline phosphatase elevation can be divided into four categories: chronic inflammation involving the bile ducts (eg, as in primary biliary cirrhosis and primary sclerosing cholangitis), infiltrative process (eg, neoplasm, tuberculosis), cholestatic disease (eg, drug hepatotoxicity), or biliary obstruction (eg, due to neoplasia or cholelithiasis).

Only a few studies have investigated the significance of a mild, isolated alkaline phosphatase elevation. Lieberman et al[16] evaluated 87 patients, finding that the abnormality resolved completely in less than 3 months in 28 patients, while in another 17 patients it had resolved in 3 to 12 months. Of the remaining 42 patients, 24 did not undergo further evaluation due to significant coexisting disease. Of the remaining 18 patients, 5 had phenytoin-related hepatotoxicity, 3 had congestive heart failure, 3 had metabolic bone disease, 2 had hepatobiliary disease, 1 had metastatic bone disease, and in 4 no explanation was found. Follow-up was 1.5 to 3 years.

Clinical workup. An isolated elevated alkaline phosphatase level should always be confirmed and a hepatic origin suspected if the gamma-glutamyl transferase level is also elevated (FIGURE 2). History of recent drug or medication exposure usually points to drug hepatotoxicity as the source of this abnormality.

Similarly, other historical data can point to the potential underlying pathologic process responsible for this rise in alkaline phosphatase. For example, a history of ulcerative colitis suggests primary sclerosing cholangitis, and history of previous cancer or sarcoidosis can suggest liver involvement. As a part of the initial evaluation, an imaging study (such as ultrasound) will exclude biliary obstruction or an infiltrative process.

If alcohol or medication is suspected, the alkaline phosphatase level should be determined again after the patient has abstained from these agents for approximately 6 to 8 weeks. If the initial examination suggests a specific disease, disease-specific markers (antimitochondrial antibody for primary biliary cirrhosis and viral serology) can confirm the suspected diagnosis. If the disease-specific markers are negative and the alkaline phosphatase level does not return to normal, further studies, including a liver biopsy and endoscopic retrograde cholangiopancreatography, should be considered.

Hepatobiliary diseases can cause moderate to marked rises in alkaline phosphatase levels

Gamma-glutamyl transferase elevation

Causes of gamma-glutamyl transferase elavation. Gamma-glutamyl transferase is a membrane enzyme that is a marker of hepatobiliary disease. Increases in gamma-glutamyl transferase usually parallel the elevation of alkaline phosphatase, confirming the hepatic source of the latter. Although gamma-glutamyl transferase is the most sensitive marker of biliary tract disease, it lacks specificity. Alcohol and a variety of drugs, such as phenytoin and phenobarbital, induce gamma-glutamyl transferase. In one study of patients with alcoholic liver disease, it was elevated in 52% of patients without known liver disease. The gamma-glutamyl transferase level can be used to monitor abstinence from alcohol in

patients with alcoholic liver disease.[17]

Clinical workup. Due to the lack of specificity and the highly inducible property of this enzyme, an extensive evaluation of an isolated gamma-glutamyl transferase elevation in an otherwise asymptomatic individual is not warranted.

CONCLUSION

A great deal of the evaluations discussed in this paper and other similar papers[18–21] can be carried out by the primary care provider following a systematic approach. A gastroenterologist's input can be valuable in patients in whom the initial workup fails to establish the diagnosis, as well as in assuring that the most effective therapy for a specific disease is instituted. Reassurance, patient education, and a systematic approach for evaluating these abnormalities will identify most treatable causes of liver disease in the most cost-effective and efficient manner.

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ADDRESS: *Zobair M. Younossi, MD, MPH, Department of Gastroenterology, S40, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195.*