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Liver Function Tests

Their Role in the Diagnosis of Hepatobiliary Diseases

Abstract

Liver diseases are common, and currently represent the 12th leading cause of death in the United States. However, numerous hepatic disorders exist, and differential diagnosis often is difficult. Moreover, because laboratory testing is routine, an abnormal serum transaminase or alkaline phosphatase in patients without clinical symptoms is not uncommon. Although liver function tests are critical in recognizing the presence of liver disease and its specific diagnosis, the interpretation of the tests may be confusing and difficult. Furthermore, not all persons with one or more test abnormalities actually have liver disease. In this review, liver function tests and an approach to their interpretation are discussed.

Chronic liver disease is the 12th most common cause of death in the United States.[1] Although hepatic diseases are relatively common, most are clinically silent, and therefore may go undetected for many years. Late-stage complications of chronic liver disease, such as hepatocellular carcinoma and cirrhosis, have increased two- to threefold over the past 20 years. Moreover, they are expected to increase another two- to threefold over the next 20 years.[2] The major causes of liver disease include excess chronic alcohol consumption, nonalcoholic steatohepatitis, and viral diseases (mainly hepatitis A, B, and C). Other important etiologic causes include genetic, malignant, metabolic, and autoimmune disorders; therapeutic drugs; and various hepatotoxins (Table 1).

Because the etiology of some liver diseases is age-related, it often is clinically useful to focus initially on these causes for patients with liver disease (Table 2).

• LIVER FUNCTION TESTS

Laboratory tests that reflect liver disease generally are termed "liver function tests." The term, however, is a misnomer, representing a broad and somewhat loose classification. Indeed, the designation "liver function tests" preceded enzyme tests and viral markers and referred to tests that truly were functional and included bilirubin, bilirubin conjugation, bromsulphthalein and

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TABLE 1

Acute and Chronic Liver Diseases/Disorders

Acute Diseases
- Viral hepatitis (A, B, C, D, E, G, cytomegalovirus, others)
- Toxic hepatitis (drugs, chemicals, pesticides, metallic compounds)
- Alcoholic hepatitis
- Others (syphilis, rubeola, Reye's Syndrome, infectious mononucleosis)

Chronic Diseases
- Alcoholic hepatitis
- Alcoholic cirrhosis
- Non-alcoholic cirrhosis (cardiac, biliary)
- Non-alcoholic steatohepatitis
- Autoimmune disorders
- Genetic disorders (hemochromatosis, Wilson's disease, alpha-1-antitrypsin deficiency, Crigler-Najjar, others)

Cholestasis/Space Occupying Lesions

Intrahepatic
- Diffuse (drugs, biliary cirrhosis, acute viral hepatitis, parenteral nutrition, primary sclerosing cholangitis, autoimmune cholangiopathy)
- Focal

Benign/Infectious (granuloma, abscess)

Malignant (hepatoma, metastatic carcinoma, lymphoma)

Extrahepatic
- Benign (common duct stone, enlarged lymph nodes)
- Malignant (pancreas, gall bladder, bile duct)
- Extrahepatic biliary atresia

TABLE 2

Selected Age-Related Causes of Liver Diseases

Neonates
- Cytomegalovirus
- Rubeola
- Herpes
- "Giant cell"
- Syphilis
- Crigler-Najjar syndrome
- Dubin-Johnson syndrome
- Rotor's syndrome

Childhood/Adolescence
- Hepatitis A, B, C
- Infectious mononucleosis
- Reye's syndrome
- Drugs/chemicals
- Gilbert's syndrome
- Wilson's disease

Adults
- Hepatitis A, B, C, D, E, G
- Ethyl alcohol
- Non-alcoholic steatosis/steatohepatitis (NASH)
- Genetic disorders (hemochromatosis, Wilson's disease, Others)
- Gilbert's syndrome
- Drugs/chemicals

cardiogreen dye tests, cephalin flocculation, and thymol turbidity. Currently, the common tests available for measuring function are assessments of bilirubin (direct and total), albumin, transthyretin (prealbumin), and prothrombin time. Moreover, the serum albumin level, bilirubin concentration, and prothrombin time all can be affected by extrahepatic factors such as protein malnutrition, hemolysis, and antibiotic use. Nevertheless, the term "liver function tests" still is commonly used (Table 3). Routine chemistry liver function panels usually consist of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), lactate dehydrogenase (LD), gamma-glutamyltransferase (GGT), bilirubin (total and conjugated), and albumin.

TABLE 3

Liver Function Tests

"Function"	Tests
Cell injury/necrosis	Alanine aminotransferase (ALT), aspartate amino-transferase (AST), AST/ALT ratio, lactate dehydrogenase (LD)
Cholestasis/space occupying lesions	Alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), leucine aminopeptidase (LAP), 5′-Nucleotidase (5′-N), bilirubin, cholesterol
Protein synthesis	Albumin, pre-albumin, prothrombin time, partial thromboplastin time
Viral markers	IgM anti-HBc, HBsAg, IgM anti-HAV, anti-HCV, HCV RNA.

• CLINICAL ASSESSMENT

In addition to a complete medical history and physical examination, emphasis during clinical assessment should

focus on alcohol consumption, risk factors for viral hepatitis (sexual promiscuity, homosexual relationships, intravenous drug use, tattoos, nonsterile ear or body piercing, blood transfusions), medications, vitamin use (vitamins A and B3), herbal or alternative remedies, and occupational exposures. Other important factors include diabetes, hyperlipidemia, and body weight (steatohepatitis), as well as a history of possible inherited diseases (Wilson's disease, hemochromatosis, alpha-1-antitrypsin deficiency) and autoimmune disorders.

• CAUSES OF INCREASED AMINOTRANSFERASE LEVELS

Both ALT and AST are very sensitive indicators of liver cell injury. As such, they are very helpful in the diagnosis of various hepatocellular diseases, including acute and chronic hepatitis (viral, alcoholic, hypoxic, toxic). Indeed, it often is difficult to diagnose hepatitis without an increase in one or both of these enzymes.

Although AST and ALT are both sensitive indicators of hepatocellular damage, they are nonspecific, especially AST (Table 4), which is found in decreasing order in the liver, heart, skeletal muscle, kidneys, pancreas, lungs, leukocytes, and erythrocytes.[3] For example, erythrocyte AST levels are 10 to 15 times that of serum. Hence, mild elevations may be attributable to hemolysis. Moreover, increased levels of AST may indicate hemolytic anemia, rhabdomyolysis, increased leukocyte count, and the like. For liver disease, ALT is a more specific indicator than AST. Although ALT is present primarily in the liver and kidney, significantly lesser amounts are present in the heart, skeletal muscle, and other tissues. Moreover, ALT is exclusively in the cell cytoplasm, whereas AST is present in both cytoplasm and mitochondria.[4] This explains why AST is more sensitive and specific for alcoholic liver disease than ALT (see the Alcoholic Liver Disease section).

TABLE 4

Causes of Increased Aminotransferases

Acute and chronic alcoholic hepatitis and cirrhosis
Medications
Viral hepatitis (A, B, C, others)
Nonalcoholic steatohepatitis (NASH)
Congestive heart failure (hypoxic injury)
Neutrophilic leukocytosis
Skeletal muscle disorders (rhabdomyolysis, genetic)
Autoimmune hepatitis
Celiac disease
Hemochromatosis
Wilson's disease
Alpha-1-antitrypsin deficiency

In the interpretation of elevated enzyme levels, it often is helpful to consider their relative degree of elevation (ie, enzyme level divided by the upper reference level). That is, the interpretation should determine whether the enzyme level is 2, 5, 10, or more times the upper reference level. It is common to overestimate the degree of elevation for some enzymes (eg, LD and ALP), and to underestimate the degree of AST and ALT elevation. For example, the upper reference level for LD is approximately 200 U/l. Thus, a value of 400 U/l is twice the normal value. However, the upper reference level of AST and ALT is 30 to 40 U/l, and 400 U/l is at least 10 times the normal level.

• ALCOHOLIC LIVER DISEASE

Patients with alcoholic liver disease exhibit a wide range of clinical features ranging from asymptomatic hepatomegaly and minimal liver function test abnormalities to severe liver disease with jaundice, coagulation problems, fever, leukocytosis, ascites, kidney failure, and encephalopathy. Although a reliable history of excess alcohol consumption is very useful, it usually is quite difficult to obtain. However, an AST level exceeding that of ALT is suggestive of alcohol abuse, especially if the AST-ALT ratio (DeRitis ratio) is two or more. In cases of alcoholic liver disease, the mitochondria are damaged (Mallory bodies), thereby releasing AST, which is added to that released from the cytoplasm. Indeed, in cases of mild alcoholic liver disease, the AST level may be 1½ to 2 times the normal level, whereas the ALT level is normal.

The levels of AST and ALT usually are less than 3 to 4 times the normal level in cases of alcoholic liver disease, but may exceed 10 times the normal level under certain conditions. For example, a patient with alcoholic hepatitis who has not eaten for a day or so and has taken acetaminophen may have extremely high AST levels (20 or more times the normal level).[5] The total bilirubin level may exceed 10 mg/dl. Moreover, if these patients have a prothrombin time 8 seconds or more beyond the control value, the prognosis generally is poor. Other poor prognostic signs include a falling AST or ALT level and a rising bilirubin concentration in patients who are not clinically improving.

Although LD often is mildly elevated in most cases of alcoholic hepatitis (2 times the normal level or less), it is not a sensitive indicator of liver disease. It also is widely distributed through all organs and tissues. For example, it is 100 or more times more concentrated in erythrocytes than in serum. Hence, even mild hemolysis

elevates the serum level. However, LD isoenzymes are more sensitive and specific for liver disease, with both LD4 and LD5 increased. In cases of alcoholic hepatitis, GGT also is commonly increased. Moreover, it is increased in most, albeit not all, patients who do not have hepatitis, but who chronically abuse alcohol. Indeed, it may be the only abnormal test in the liver profile. However, GGT is not increased after a single binge. An increased GGT level also is commonly observed in patients receiving chronic antiepileptic medication (eg, Dilantin, phenobarbital, Mysoline, Zarontin).

The total bilirubin level is normal or mildly elevated in most cases of alcoholic hepatitis unless the disease is somewhat advanced, in which case it may reach 7 mg/dl or higher. In the absence of obstruction, the mortality rate increases progressively as the total bilirubin rises above 7 mg/dl. Conjugated bilirubin ranges from 20% to 60% of the total bilirubin level in most cases of hepatocellular disease.

Normally, the serum albumin level is higher than the total globulin level. However, in cases of chronic alcoholic hepatitis and other forms of chronic liver disease, the serum albumin level is decreased (less than 4 g/dl) and the globulin level is increased (albumin-total protein ratio, <0.5). In cases of chronic liver disease, a diagnosis of cirrhosis often can be distinguished by serum electrophoresis, which exhibits not only an albumin-total protein ratio less than 0.5, but also "beta-gamma bridging." That is, the normal "valley" between the beta and gamma globulins is eliminated because of increased immunoglobulin A synthesis, which is present between the beta and gamma globulin fractions.

• NONALCOHOLIC STEATOHEPATITIS

Until very recently, nonalcoholic steatohepatitis (NASH), also known as nonalcoholic fatty liver disease, was considered relatively uncommon. The term "nonalcoholic steatohepatitis" was coined to describe "the pathological and clinical features of nonalcoholic disease of the liver associated with the pathological features most commonly seen in alcoholic liver disease itself."[6(p434)] Indeed, liver biopsy results in cases of NASH generally simulate those for alcoholic hepatitis (increased fat, inflammatory cells, and variable fibrosis). Currently, NASH may be the most common liver disorder after hepatitis C (HCV) among patients presenting with persistently abnormal liver function tests.[7] As with alcoholic hepatitis, patients with NASH have increased AST and ALT levels. However, the AST-ALT ratio is less than 1 in the phases before fibrosis or cirrhosis.

The major risk factors for NASH include obesity, impaired glucose intolerance or type 2 diabetes, hypertension, and hypertriglyceridemia, but a negative history of excess alcohol intake. Although early obesity studies suggested that approximately 75% of individuals with NASH were female, more recent studies indicate that about half are male.[8] The cited author has referred to NASH as "another disease of affluence."

Others have studied the association between elevated liver enzymes and total body fat in otherwise healthy obese persons.[9] Their results show a progressive increase in AST, ALT, and GGT with total body fat, especially above the 75th percentile, in both men and women. However, the enzyme levels were higher in men than in women.

• VIRAL HEPATITIS

Since the introduction of vaccines for hepatitis A and B and the routine testing of the blood supply for HCV, the incidence of acute viral hepatitis has decreased significantly. Nevertheless, an estimated 300 to 500 million people worldwide (5-6% of the population) have chronic hepatitis B, and approximately 1 to 1.25 million of these are American citizens. Moreover, about 170 million people (3% of the world population) have chronic HCV, and an estimated 2.1 to 2.8 million of these are United States residents.[10] Indeed, "almost 100,000 cases of HCV occur annually in the United States alone, most of them undiagnosed."[11] Persons with chronic hepatitis are at a significantly increased risk for the development of cirrhosis and liver cancer, the major causes of death from liver disease in the United States and other Western countries.[11]

In individuals of viral hepatitis, ALT and AST serum levels begin to rise, then peak near the onset of jaundice, after which they gradually begin to fall.[12] However, AST and ALT levels vary greatly in these individuals. Early on and later in the disease, AST and ALT levels may be only 1½ to 2 times the normal level, although they commonly reach 10 or more times normal at their peak. Moreover, in cases of severe viral hepatitis, an AST-ALT ratio of 2 or more is associated with an increased risk of mortality.[13] In the current study, almost 50% of the patients with severe viral hepatitis died. The mean AST-ALT ratio for the females who died was 2.05, as compared with 0.45 for those who lived. For the males, the AST-ALT ratios were 1.01 and 0.45, respectively. Others also have reported progressive liver functional impairment with an increase in the AST-ALT ratio.[14] These authors concluded that the AST-ALT ratio "is useful to differentiate mild from moderate and severe degrees of disease at a particular

point in time."[14(p1252)] Although mild AST and ALt elevations are present in most cases of subclinical viral hepatitis, the individuals often are unaware that they have the disease. In this, HCV differs significantly from the other types of viral hepatitis. For example, in a group of 100 consecutive blood donors with elevated ALT levels, 17% had HCV (48% had changes related to alcohol abuse and 22% had a fatty liver).[15] Moreover, HCV-positive individuals with repeatedly normal ALT levels have less severe disease,[16] and 6% to 8% have normal liver biopsy results.[17] Nevertheless, up to 20% of HCV-infected individuals with repeatedly normal ALT values have chronic active hepatitis, including hepatic fibrosis and cirrhosis.[18] Furthermore, the higher the ALT level, the more rapid the development of cirrhosis and hepatocellular carcinoma.[19]

As with alcoholic hepatitis, LD may be normal or modestly elevated, with increased LD4 and LD5 on serum protein electrophoresis. In addition, GGT may be increased depending to some extent on the basis of intrahepatic obstruction. Likewise, the total serum bilirubin level may be normal or increased in viral hepatitis, depending on the severity of the disease. However, conjugated bilirubin may represent 70% or more of the total bilirubin because intrahepatic bile stasis is common.

• CONGESTIVE HEART FAILURE (HYPOXIA-ISCHEMIA)

Congestive heart failure results in poor hepatic circulation, with resultant liver hypoxia and hepatocellular injury and necrosis. In such cases, liver function tests produce a hepatitis-like picture. However, correct identification of the cause for the elevated aminotransferases in these cases often is clinically difficult and commonly goes undiagnosed. For example, in a study of 137 patients with AST levels of 400 U/l or more (10 or more times normal), ischemia-hypoxia was the cause in 68 cases (49.6%).[20] The second most common cause of marked AST elevation was pancreatobiliary disease (33 cases). Primary liver disease was present in only 23 cases. Unfortunately, only 48% of the patients were correctly diagnosed, and the elevated AST levels were "apparently not noticed by the attending clinicians" in 38% of the cases.

• DRUGS, MEDICATIONS, HERBS, AND SUBSTANCE ABUSE

In addition to the more common causes of increased aminotransferase levels, (eg, alcohol, viruses, NASH, congestive heart failure), prescribed medicines, accidental or intentional ingestion, and other exposures to liver toxins are increasingly common causes. Therefore, a careful clinical history and a critical review of the laboratory data are critical. Certainly, liver toxicity is a possibility if the increase in aminotransferase levels is associated with the initiation of a therapeutic medication or exposure to environmental chemicals, herbal toxins, or drugs of abuse (Table 5).[21-23]

Although numerous reports indicate that increased transaminase levels are associated with anabolic steroid abuse, this association may have been overstated.[24] Indeed, at least some of the elevated aminotransferase levels may have been attributable to muscle injury. Therefore, for persons taking anabolic steroids who have increased transaminase levels, serum creatine kinase and GGT "should be considered in addition to ALT and AST levels as essential elements of assessment."[24(p34)] In such cases, an increased creatine kinase level would indicate muscle injury, whereas an elevated GGT level would support a diagnosis of liver damage.

• GENETIC DISORDERS

Increased aminotransferase levels may be present in cases of hereditary hemochromatosis, a relatively common autosomal recessive disorder.[25] Indeed, about 1 in 10

TABLE 5

Selected Chemical and Drug Hepatotoxins

- Hypervitaminosis A, B3
- Ethyl alcohol
- Medications
  - Acetaminophen
  - Antibiotics
  - Antiepileptics
  - Nonsteroidal antiinflammatory
  - Heparin
  - Simvastatin
  - Lovastatin
  - Pravastatin
- Aromatic hydrocarbons
  - Benzene
  - Toluene
  - Zylene
- Drugs and substances of abuse
  - Anabolic steroids
  - Cocaine
  - "Ecstasy"
  - Phencyclidine
  - Others
- Mushrooms (Amanta phalloides)
- Transition metals
  - As, Be, Cd, Cu, Pb
- Halogenated hydrocarbons
  - Chloroform
  - Carbon tetrachloride
  - Polychlorinated biphenyls
  - Halothane
  - Tetrachloroethene
- Herbs and homeopathic treatments
  - Chaparral
  - Germander
  - Senna
  - Comfrey
  - Pennyroyal
- Pesticides
  - Chlordecone
  - Dioxin
  - Hexachlorobenzene
  - Diquat
  - Paraquat
- Nitro compounds
  - Dinitrobenzene
  - Trinitrotoluene

white people carry the gene, and approximately 1 in 200 have the disease.

Screening for hemochromatosis is cost effective and begins with the measurement of serum iron and iron-binding capacity. A transferrin saturation value (serum iron divided by iron-binding capacity) of 45% or more is suggestive and should lead to further studies (ie, liver biopsy to assess liver iron levels and disease severity). The serum ferritin level also may be helpful, but because it is an acute inflammatory marker, false-positive results are possible. Although the need for liver biopsy has decreased since genetic testing became available, biopsy remains the "gold standard" for assessing the degree of fibrosis and the possibility of future carcinoma.

Wilson's disease, a recessive genetic disorder of biliary copper excretion, may present with increased aminotransferase levels. Although the clinical onset usually occurs in 5 to 25 years, it may not occur until about 40 years later. If the disease is suspected, the initial test should be serum ceruloplasmin, which shows reduced levels in about 85% of cases. Low serum copper levels also are present. Subsequent tests may include ophthalmic examination for Kaiser-Fleischer rings, copper measurement in a 24-hour urine specimen, and liver biopsy for copper evaluation.

Serum aminotransferase levels also are commonly increased in alpha-1-antitryhpsin deficiency, a rare recessive disorder that presents in early childhood. Serum protein electrophoresis usually shows decreased alpha globulin bands. The diagnosis is best established by genetic testing.

• AUTOIMMUNE HEPATITIS

Autoimmune hepatitis is an uncommon cause of increased aminotransferase levels. It primarily affects young to middle-aged women,[26] and the female-to-male ratio is 4 to 1.[3] The serum albumin level commonly is decreased, whereas the gamma globulin level is increased. Normally, the serum albumin level is higher than the total globulin level (total protein minus albumin equals globulins). If the total globulin level equals or exceeds the albumin level, a serum protein electrophoresis is useful. As with cirrhosis and various granulomatous diseases, there is a polyclonal gammopathy (ie, increase in gamma globulins). An antinuclear antibody result greater than 1:160 and a positive smooth muscle antibody test indicate an autoimmune disease.

• CAUSES OF INCREASED BILIRUBIN

Bilirubin is the end product of erythrocyte turnover in the reticuloendothelial system. Unconjugated bilirubin ("indirect bilirubin") is transported to the liver loosely bound to albumin because it is water insoluble and cannot be excreted directly in the urine. It is conjugated in the liver to form bilirubin glucuronide ("direct bilirubin"), which is water soluble and secreted into bile, some of which is reabsorbed from the gut into the circulation. Hence, total bilirubin is normally about 80% unconjugated. Increased unconjugated bilirubin levels may be present in several nonhepatic disorders including hemolytic anemia, ineffective erythropoiesis, resorption of a hematoma, and muscle injury aftermath, among others (Table 6). In these cases, unconjugated bilirubin usually exceeds 80% of the total bilirubin.

Conjugated bilirubin normally is increased (20-60%) in most hepatocellular diseases and exceeds 70% in both intrahepatic and extrahepatic obstruction of the biliary tract (cholestasis). Moreover, conjugated bilirubin may be 70% or more in some cases of viral hepatitis attributable to intrahepatic cholestasis. Thus, evaluation of the conjugated bilirubin-total bilirubin ratio often is useful in the differential diagnosis of hyperbilirubinemia. That is, a ratio less than 20% suggests a prehepatic disorder; a 20% to 70% ratio suggests a hepatocellular disease; and more than a 70% ratio suggests posthepatic cholestasis (also some cases of viral hepatitis).

• CAUSES OF INCREASED UNCONJUGATED BILIRUBIN

In addition to the aforementioned nonhepatic disorders, unconjugated hyperbilirubinemia (≥80% of total bilirubin) occurs with disorders in which either bilirubin

TABLE 6

Causes of Hyperbilirubinemia

Unconjugated Bilirubin
Increased bilirubin synthesis
Hemolytic anemia
Ineffective erythropoiesis
Pulmonary embolism with infarction
Resorption of large hematoma
Decreased Liver Uptake/Conjugation
Neonatal jaundice
Gilbert's syndrome
Fasting 40 or more hours
Criggler-Najjar syndromes (I and II)
Conjugated Bilirubin
Hepatocellular diseases
Intra- and extrahepatic bile stasis
Dubin-Johnson syndrome
Rotor's syndrome

synthesis is increased or there are defects in hepatic uptake or conjugation, which may be inherited or acquired. The most common causes of prehepatic hyperbilirubinema are neonatal jaundice, Gilbert's syndrome, and prolonged fasting.

The most common form of unconjugated hyperbilirubinemia is seen in the neonate (physiologic jaundice). Most full-term newborns have unconjugated bilirubin levels in the 4 to 5 mg/dl range, although the level may be as high as 10 mg/dl or more within the first 48 hours, after which it returns to normal within 7 to 10 days. The bilirubin levels may be higher in premature neonates. This temporary increase is caused by increased bilirubin production attributable to erythrocyte hemolysis and incomplete maturation of the bilirubin metabolism and excretion systems.

Gilbert's syndrome, a common familial disorder occurring in about 6% of the population, is frequently not recognized. It is a heterogeneous condition generally ascribed to decreased UDP-glucuronyltransferase, but it also may be attributable to defects in cell membrane transport. Although it is a bland disorder, diagnosis is important to prevent future diagnostic confusion and extensive unnecessary testing, including a possible liver biopsy. The total bilirubin level usually is 1.5 to 3 mg/dl, although during an acute illness or after prolonged fasting, the total bilirubin level may exceed 6 mg/dl.

Fasting hyperbilirubinemia has been well recognized for many years.[27] With this condition, the total bilirubin level becomes approximately twice the baseline level, resulting in mild hyperbilirubinemia. However, this phenomenon often goes unrecognized. After hospital admission and successful parenteral or oral nutrition, the level returns to normal within approximately 2 to 4 hours, and the initial report is incorrectly designated a "lab error."

Other, albeit rare, causes of unconjugated hyperbilirubinemia are types 1 and 2 Crigler-Najjar syndromes. With the type 1 syndrome, the enzyme UDP-glutamyltransferase is totally absent, whereas with the type 2 syndrome, the enzyme is reduced but still measurable. Type 1 Crigler-Najjar syndrome is characterized by extremely high bilirubin levels, resulting in kernicterus and death.

• CAUSES OF INCREASED CONJUGATED BILIRUBIN

Whereas total bilirubin is a relatively nonspecific and insensitive measurement of liver disease, conjugated bilirubin is significantly more sensitive and specific. Indeed, conjugated bilirubin may be the only abnormal test in cases of inactive cirrhosis. In most cases of hepatocellular disease with increased total bilirubin, the unconjugated fraction constitutes 20% to 60% of the total bilirubin, although it may be 70% or more in some cases of viral hepatitis and drug- or steroid hormone-induced cholestasis. Conjugated bilirubin also is significantly increased in extrahepatic obstructive disorders including common bile duct stone, carcinoma of the pancreas, extrahepatic biliary atresia, locally enlarged lymph nodes, and sclerosing cholangitis. It also is increased in the genetic recessive disorders, Rotor's and Dubin-Johnson syndromes, both of which are bland conditions.

• CAUSES OF INCREASED CHOLESTATIC ENZYMES

Leucine aminopeptidase, ALP, GGT, and 5′-nucleotidase are commonly designated as cholestatic enzymes, although they also are significantly increased in space-occupying lesions and various physiologic conditions (Table 7). Because the measurement of 5′-nucleotidase and leucine aminopeptidase is not routinely available in most laboratories and adds little to the diagnosis of hepatic disorders, it is not discussed in this review.

TABLE 7

Causes of Increased Cholestatic Enzymes

Physiologic/Genetic
Benign, physiologic (intestinal ALP)
Infancy/early childhood
Adolescence (ALP)
Pregnancy, third trimester (ALP)
Postmenopausal women (ALP)
Hyperphosphatasemia of infancy and early childhood
Benign familial hyperphosphatasemia
Chronic alcoholism, chronic antiepileptic drug use (GGT)
Pathological
Hepatocellular diseases (alcoholic, viral, etc)
Pancreatic carcinoma
Common bile duct stone or stricture
Space occupying lesions [granulomas (TB, sarcoid, others), tumors]
Sclerosing cholangitis
Primary biliary cirrhosis
Extrahepatic biliary atresia
Drug-induced cholestasis (phenothiazines, erythromycin, others)
Bone diseases/disorders (ALP)

ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase.

• ALKALINE PHOSPHATASE

Alkaline phosphatase (ALP) is present in liver, bone, intestine, kidney, neutrophils, and placenta. Although about 80% of serum ALP originates from the liver and bone, clinicians must recognize other common sources of increased ALP levels because they may be either physiologic or pathologic. Examples of physiologic and genetic ALP elevations are as follows. Women in their third trimester of pregnancy have increased ALP levels attributable to the release of placental ALP. Moreover, some persons with blood type O or B who are secretors may have increased intestinal ALP after a fatty meal. Therefore, for appropriate interpretation, it is critical that patients fast before testing.

Other physiologic and genetic conditions associated with increased ALP levels are hyperphosphatasemia of infancy and early childhood[28,29] and benign familial hyperphosphatasemia.[30,31] The latter condition is an uncommon, benign, and presumably dominant inherited disorder. Fasting ALP levels usually are two to four times higher than the normal level. Although intestinal ALP is the major isoenzyme, bone and liver isoenzymes may also be increased. Hyperphosphatasemia of infancy and early childhood, an uncommon benign disorder of unknown etiology, may occur more frequently than realized because children are not commonly tested for ALP. The levels usually return to normal within 3 to 4 months. Typically, ALP elevations are more than five times the upper adult level and occur in children younger than 5 years. There are no known negative sequelae.

Age also is a very important factor in the interpretation of an elevated ALP. From infancy through early childhood, ALP levels average about twice the adult level. During puberty, ALP levels may be three or more times higher.[32] Adolescent girls reach adult levels by the age of 14 to 16 years, and boys reach adult levels by the age of 18 to 20 years. The elevated ALP levels during childhood and adolescence are of bone origin. Moreover, serum levels rise gradually in women about 40 to 65 years of age, and are about 50% higher at the age of 65 years than at the age of 30 years.[33] Additionally, ALP levels are increased in smokers and in overweight and obese individuals (see the sections on steatohepatitis and transaminases).

In patients with an increased ALP level for whom there is question as to its origin, measurement of GGT often is very helpful. If the GGT is increased, the ALP source is most likely the liver. If the GGT is normal, the increased ALP most likely originates in bone, but may also be from another source (Figure 1). Although tests involving heat or urea denaturation of serum ALP are offered by many laboratories, neither is sensitive or specific.

Alkaline phosphatase values may be five or more times the upper reference level when bile flow is impaired or when space-occupying lesions (tuberculosis, sarcoid, other granulomas, primary or metastatic tumors) are present. Lesser elevations (2-3 times the upper reference level) are common as well as parallel conjugated bilirubin in both intra- and extrahepatic cholestasis. In partial obstruction, ALP rises as much as it does with complete obstruction, although bilirubin does not. In most cholestatic disorders, AST or ALT is mildly increased. However, cholestasis with cholangitis results in substantially elevated transaminase levels.

• GAMMA-GLUTAMYLTRANSFERASE

Gamma-glutamyltransferase (GGT) is found in both hepatocytes and biliary epithelial cells. It is significantly more specific for hepatobiliary disease than ALP because it is not increased in bone, placenta, intestine, leukocytes, or secretors with blood types O or B. Moreover, although increased levels are present in infants up to about 6 months of age, it is not increased in adolescents or postmenopausal women.[34] Thus, as previously noted, the major value of GGT is its ability to confirm that an increased ALP is of hepatic origin (Figure 1).

Nevertheless, GGT lacks specificity, being increased in pancreatic disease, myocardial infarction, kidney failure, and chronic obstructive lung disease.[35] Because GGT is an inducible microsomal enzyme, increased serum levels are commonly present in individuals receiving long-term antiepileptic drugs (eg, Zarontin, phenobarbital, phenytoin).[36] Moreover, GGT has been advocated for identifying

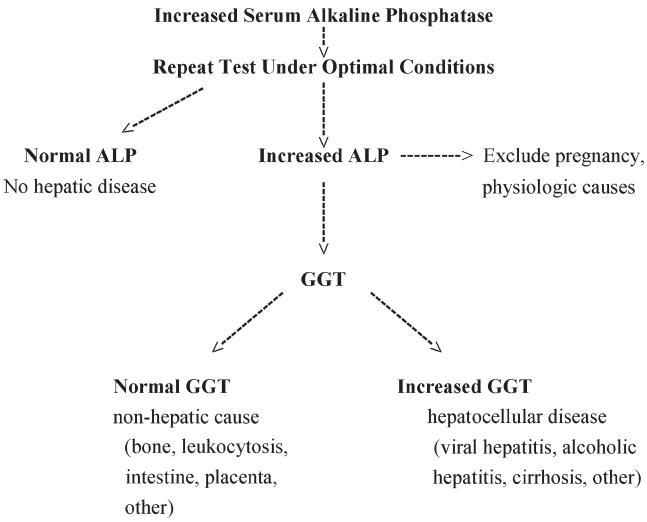


FIGURE **1.**
Algorithmic approach to patients with isolated increased serum ALP.

patients with unreported excess alcohol use.[37-40] Indeed, the sensitivity of an elevated serum GGT in these cases has ranged from 52% to 94%.

• ALBUMIN

Serum albumin is synthesized exclusively by the liver and has a circulating half-life of 18 to 20 days. For patients with hepatocellular diseases, albumin is a useful marker of both chronicity and severity. As levels fall below 2.8 g/dl, the mortality rate progressively increases such that the prognosis is poor for those whose serum albumin is 2 g/dl or less. The preoperative serum albumin level also is an excellent predictor of operative mortality and morbidity.[41] In this large multiple Veteran's Administration study involving 54,215 major noncardiac surgery cases, the authors concluded that "serum albumin concentration is a better predictor of surgical outcomes than many other preoperative patient characteristics."[41(p36)] Albumin is not, however, a highly specific marker of liver disease. Indeed, low levels of albumin are present in various acute inflammatory disorders and in various chronic diseases such as rheumatoid arthritis, systemic lupus, and various granulomatous diseases (eg, tuberculosis, sarcoidosis, histoplasmosis). It also is decreased in many elderly patients who are protein malnourished, a very common but often unrecognized problem.

• PROTHROMBIN TIME

Clotting factors 2 (prothrombin), 7, 9, and 10 are vitamin K dependent. If vitamin K is not absorbed because of cholestasis, or in patients with hepatocellular disease, the prothrombin time is prolonged. If the prolonged prothrombin time is attributable to cholestasis, a correction of 30% or more is noted within about 24 hours after parenteral administration of vitamin K. The prothrombin time also may be prolonged in patients with steatorrhea or those with inadequate vitamin K dietary intake. As with albumin, the prothrombin time is a useful prognostic marker for patients with hepatocellular disease. Thus, a prothrombin time 8 seconds or more beyond the control value indicates a progressive decrease in prognosis.

• OTHER TESTS

Lactate dehydrogenase (LD) is a widely disseminated enzyme present in essentially all tissues and organs. Because it commonly is included in the "routine" chemistry profile, it often is mildly increased in hepatobiliary disorders when the transaminases are significantly elevated. Although increased in a wide variety of disorders, LD lacks both sensitivity and specificity. However, there are five LD isoenzymes. Hence, a significant increase in LD5 and LD4, as shown by electrophoresis, is supportive of liver disease and may be useful when the cause of elevated transaminases is not clear.

The most characteristic laboratory findings in acute viral hepatitis are increased levels of serum transaminases, which are commonly 10 or more times the upper reference level. Levels exceeding 100 times the normal level have been reported.[42] However, with HCV, all enzymes may be in the normal range.[15,43] Although the history and physical examination may suggest risk factors for hepatitis A (eg, ingestion of contaminated food, travel to an endemic area), hepatitis B (eg, homosexuality, intravenous drug use), or hepatitis C (eg, multiple blood transfusions, intravenous drug abuse), serologic viral markers are essential. Specific laboratory testing for viral hepatitis has been recently reviewed by Sacher et al.[44]

In summary, liver function tests are critical in the diagnosis and management of hepatic diseases. Nevertheless, most of these tests are nonspecific since many of the analytes are widely distributed. Therefore, healthcare providers must be knowledgeable, not only regarding the numerous hepatic diseases and disorders, but also about the use and interpretation of liver function tests.

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