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Liver biochemical tests that detect injury to hepatocytes

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INTRODUCTION

A number of blood tests are available that reflect the condition of the liver [1,2]. The most common tests used in clinical practice include the serum aminotransferases, bilirubin, alkaline phosphatase, albumin, and prothrombin time. These tests are often referred to as "liver function tests," although this term is somewhat misleading since most do not accurately reflect how well the liver is functioning, and abnormal values can be caused by diseases unrelated to the liver. In addition, these tests may be normal in patients who have advanced liver disease [3,4] .

Several specialized tests have also been developed (such as indocyanine green clearance), which, although uncommonly used in clinical practice, can measure specific aspects of hepatic function.

Despite their limitations, liver biochemical and function tests have many applications in clinical medicine:

- They provide a noninvasive method to screen for the presence of liver disease. In the past, the serum aminotransferases, for example, were part of a panel of tests used to screen all blood donors in the United States for the presence of transmissible viruses, and they are still used for this purpose in some countries.

- They can be used to measure the efficacy of treatments for liver disease (such as immunosuppressant agents for autoimmune hepatitis). (See "Management of

autoimmune hepatitis".)

- They can be used to monitor the progression of a disease such as viral or alcohol-associated hepatitis.

- They can reflect the severity of liver disease, particularly in patients who have cirrhosis. As an example, the Child-Turcotte-Pugh score (Child-Pugh class), which incorporates the prothrombin time and serum bilirubin and albumin concentrations, can predict survival (table 1).

The pattern of abnormalities on these tests is more accurate than any of the individual tests. Elevation of serum aminotransferases indicates hepatocellular injury (which may be accompanied by elevation of the serum total bilirubin), while elevation of the alkaline phosphatase and serum total bilirubin indicates cholestasis. Recognition of patterns that are consistent with specific diseases can prompt appropriate additional testing.

The liver biochemical and function tests can be categorized as follows:

- Tests that detect injury to hepatocytes: Most of these tests measure the activity of hepatic enzymes, such as the aminotransferases, in the circulation. These enzymes are normally intracellular but are released when hepatocytes are injured.

- Tests of the liver's capacity to transport organic anions and metabolize drugs: These tests measure the liver's ability to clear endogenous or exogenous substances from the circulation. The best studied include serum measurements of bilirubin, bile acids, caffeine, and lidocaine metabolites, a variety of breath tests, and clearance tests such as bromsulphalein and indocyanine green.

- Tests of the liver's biosynthetic capacity: The most commonly performed tests to assess the biosynthetic capacity of the liver are the serum albumin and the prothrombin time (which requires the presence of clotting factors produced in the liver). Other tests that are used are the serum concentrations of lipoproteins, ceruloplasmin, ferritin, and alpha-1 antitrypsin.

- Tests that detect chronic inflammation in the liver, altered immunoregulation, or viral hepatitis: These tests include the immunoglobulins, hepatitis serologies, and specific autoantibodies. Most of these substances are proteins made by B lymphocytes, not by hepatocytes. However, some are quite specific for certain liver diseases, such as antimitochondrial antibodies in primary biliary cholangitis. (See "Clinical manifestations, diagnosis, and prognosis of primary biliary cholangitis".)

The liver contains thousands of enzymes, some of which are also present in serum in very low concentrations. Elevation of an enzyme activity in the serum primarily reflects release from damaged liver cells. Elevation of serum enzyme tests can be grouped into two categories:

- Enzymes that reflect generalized damage to hepatocytes
- Enzymes that reflect cholestasis

This topic will review the tests that detect injury to hepatocytes. The other categories and enzymes that reflect cholestasis are discussed separately. (See "Enzymatic measures of cholestasis (eg, alkaline phosphatase, 5'-nucleotidase, gamma-glutamyl transpeptidase)".)

SERUM AMINOTRANSFERASES

The serum aminotransferases (formerly called transaminases) are sensitive indicators of liver cell injury [5-7]. The most commonly measured are alanine aminotransferase (ALT, serum glutamic-pyruvic transaminase [SGPT]) and aspartate aminotransferase (AST, serum glutamic-oxaloacetic transaminase [SGOT]). These enzymes catalyze the transfer of the alpha-amino groups of alanine and aspartate, respectively, to the alpha-keto group of ketoglutarate, which results in the formation of pyruvate and oxaloacetate.

The serum ALT and AST concentrations are normally less than 30 to 40 international unit/L (0.5001 to 0.6668 microkatal/liter), although there is some debate as to the optimal cutoff values that should be used. Several studies have shown that ALT levels are normally higher in males than females and vary directly with body mass index and, to a lesser degree, with serum lipid levels and age [8,9]. In females, ALT levels fluctuate during the normal menstrual cycle, possibly mediated by progesterone, with peak levels in the mid-follicular phase and trough levels in the late luteal phase [10] (see "Approach to the patient with abnormal liver biochemical and function tests", section on 'Common liver biochemical and function tests'). In older adults, elevation of the serum ALT level (and gamma glutamyl transpeptidase level) may be associated with all-cause and cardiovascular mortality [11], and elevation of the serum AST level and of the AST/ALT ratio may be associated with all-cause and liver-related mortality [12,13]. Levels decline in frail older adults and are inversely associated with loss of independence and death [14]. Consumption of coffee and especially caffeine may lower serum ALT and AST levels by mechanisms that are incompletely understood [15,16]. In the absence of identifiable risk factors for liver disease, the normal serum ALT level ranges from 29 to 33 international unit/L for males and 19 to 25 international unit/L for females [1].

The source of these enzymes in serum has never been clearly established, although they probably originate in tissues rich in ALT and AST. ALT is present in highest concentration in the liver [17,18]. AST is found, in decreasing order of concentration, in the liver, cardiac muscle, skeletal muscle, kidneys, brain, pancreas, spleen, lungs, leukocytes, and erythrocytes and is less specific than ALT for liver disease [19].

The location of the aminotransferases within cells is variable. ALT is found exclusively in the cytosol, whereas AST occurs in the cytosol and mitochondria [18]. The cytosolic and mitochondrial forms of AST are immunologically distinct isoenzymes, which can be distinguished by several laboratory techniques [20]. Approximately 80 percent of AST activity in human liver is derived from the mitochondrial isoenzyme [18]. In contrast, most of the circulating AST activity in healthy people is derived from the cytosolic isoenzyme [17].

Neither ALT nor AST has isoenzymes that are tissue specific. As a result, isoenzyme analysis of serum ALT or AST is of limited clinical utility. Exceptions to this general rule can occur in acute myocardial infarction and chronic (but not acute) alcohol-associated liver disease [21,22]. Large increases in mitochondrial AST occur in serum after extensive tissue necrosis, and assay of mitochondrial AST was once advocated as an accurate test for the detection of myocardial infarction [21]. However, other serum tests, such as troponins, are considered the standard for the diagnosis of myocardial infarction. (See "Troponin testing: Clinical use".)

Measurement — The activity of the serum aminotransferases reflects the rate at which they enter and are cleared from the circulation. An elevation in serum ALT and AST is usually related to damage or destruction of tissues rich in the aminotransferases or to changes in cell membrane permeability that permit leakage into the circulation.

Clearance of the serum aminotransferases is similar to that of other proteins and involves catabolism by the reticuloendothelial system; AST is cleared more rapidly than ALT [23]. The major site of AST clearance is the hepatic sinusoidal cell [24]. It is unlikely that biliary or urinary excretion has a significant role since the enzymes are virtually undetectable in the urine and present in only very small amounts in bile [23,25].

Of the numerous methods developed for measuring ALT and AST activity in serum, the most specific method involves the indirect measurement of lactate and malate (derived from the formation of pyruvate and oxaloacetate, respectively, in the aminotransferase reactions) [21]. During this reaction, the reduced form of nicotinamide-adenine dinucleotide (NADH), (the cofactor in the reaction) is oxidized to NAD. Because NADH, but not NAD, absorbs light at 340 nm, the event can be followed spectrophotometrically by the loss of absorptivity at 340 nm.

The serum aminotransferases may be falsely elevated or decreased under certain circumstances. Drugs such as erythromycin and furosemide may produce falsely elevated aminotransferase [26]. In contrast, falsely low serum AST (but not ALT) is seen in persons with renal failure or those taking isoniazid [27]. In persons with renal failure, serum AST activity increases significantly after hemodialysis, indicating removal of an inhibitor, which does not appear to be urea [27]. (See "Serum enzymes in patients with kidney failure".) Subnormal values of serum ALT have been described in patients with Crohn disease, the reason for which is unclear [28].

Clinical significance — Serum aminotransferases are elevated in most liver diseases and in disorders that involve the liver (such as various infections, nonalcoholic fatty liver disease, acute and chronic heart failure, and metastatic carcinoma). Elevations up to eight times the upper limit of normal are nonspecific and may be found in any of the above disorders. The highest elevations occur in disorders associated with extensive hepatocellular injury, such as acute viral hepatitis, ischemic hepatitis (hypoxic hepatitis, shock liver), and acute drug- or toxin-induced liver injury (eg, acetaminophen toxicity). The evaluation of the serum aminotransferases in various clinical settings, including use of the AST/ALT ratio, is discussed in detail separately. (See "Approach to the patient with abnormal liver biochemical and function tests".)

The extent of liver cell necrosis correlates poorly with the magnitude of serum aminotransferase elevation; in addition, the absolute elevation in serum aminotransferases is of little prognostic value since the liver can recover from most forms of acute injury. There is, however, one pattern that is important to recognize: a rapid decrease in plasma AST and ALT levels, together with a rise in the plasma bilirubin concentration and prolongation of the prothrombin time, is indicative of a poor prognosis in patients with acute liver failure. Although a rapid decrease in serum aminotransferases is usually a sign of recovery from disease, it may also reflect the massive destruction of viable hepatocytes in patients with acute liver failure, signaling a poor prognosis.

SERUM CONCENTRATIONS OF OTHER HEPATIC ENZYMES

A variety of other hepatic enzymes have been measured but none is as useful as the aminotransferases for the diagnosis of hepatic disease.

Lactate dehydrogenase — Lactate dehydrogenase (LDH) is a cytoplasmic enzyme present in tissues throughout the body (table 2). Five isoenzyme forms of LDH are present in serum and can be separated by various electrophoretic techniques. The slowest migrating band predominates in the liver [29,30]. This test is not as sensitive as the serum aminotransferases in

liver disease and has poor diagnostic specificity, even when isoenzyme analysis is used. In the past it was used as a marker of myocardial infarction (although no longer used for this purpose), and it is a marker of hemolysis [29] (see "Use of creatine kinase to detect myocardial injury"). In patients with acute hepatocellular injury, a markedly elevated serum LDH level distinguishes ischemic hepatitis (ALT-to-LDH ratio less than 1.5) from viral hepatitis (ALT-to-LDH ratio greater than or equal to 1.5) with a sensitivity and specificity of 94 and 84 percent, respectively [31]. An elevated serum LDH level is an adverse prognostic marker in patients with metastatic melanoma and may be the first indication of liver metastases [32].

Glutamate dehydrogenase — Glutamate dehydrogenase, a mitochondrial enzyme, is found primarily in the liver, heart, muscle and kidneys [33]. In the liver, it is present in highest concentration in centrilobular hepatocytes [34]. Because of this location, serum glutamate dehydrogenase has been evaluated as a specific marker for liver disorders, such as alcohol-associated hepatitis, that primarily affect centrilobular hepatocytes [35]. Although an initial report suggested that glutamate dehydrogenase may be a sensitive and relatively specific marker for alcohol-associated hepatitis, this observation has not been confirmed by others [5,36]. Glutamate dehydrogenase has also been studied as a biomarker for drug-induced liver injury [37]. Measurement of serum glutamate dehydrogenase is seldom performed, but its presence in stool is used as a diagnostic marker of *Clostridiosis difficile* infection [38].

Isocitrate dehydrogenase — Isocitrate dehydrogenase, a cytoplasmic enzyme, is found in the liver, heart, kidneys, and skeletal muscle [39]. Its activity in serum parallels that of the serum aminotransferases in acute and chronic hepatitis, but it is less sensitive [40,41]. Although elevations in serum isocitrate dehydrogenase are relatively specific for liver disorders, increased concentrations have been reported in disseminated malignancy without detectable hepatic involvement [42]. Measurement of this enzyme offers no diagnostic advantage over the serum aminotransferases.

Sorbitol dehydrogenase — Sorbitol dehydrogenase is a cytoplasmic enzyme found predominantly in the liver with relatively low concentrations in the prostate gland and kidneys [39]. Its activity in serum parallels that of the aminotransferases in hepatobiliary disorders. However, it appears to be less sensitive, and values may be normal in cirrhosis and other chronic liver disorders. Its instability in serum further limits its diagnostic usefulness [39].

SUMMARY AND RECOMMENDATIONS

- A number of blood tests are available that reflect the condition of the liver. The most common tests used in clinical practice include the serum aminotransferases, bilirubin,

alkaline phosphatase, albumin, and prothrombin time. These tests are often referred to as "liver function tests," although this term is somewhat misleading since most do not accurately reflect how well the liver is functioning, and abnormal values can be caused by diseases unrelated to the liver. In addition, these tests may be normal in patients who have advanced liver disease. (See "Approach to the patient with abnormal liver biochemical and function tests".)

- The serum aminotransferases (formerly called transaminases) are sensitive indicators of hepatocyte injury. The most commonly measured are alanine aminotransferase (ALT, serum glutamic-pyruvic transaminase) and aspartate aminotransferase (AST, serum glutamic-oxaloacetic transaminase). (See 'Serum aminotransferases' above.)

- Serum aminotransferases are elevated in most liver diseases and in disorders that involve the liver (such as various infections, drug toxicity, nonalcoholic fatty liver disease, acute heart failure, and metastatic carcinoma). Elevations up to eight times the upper limit of normal are nonspecific and may be found in many disorders involving the liver. The highest elevations occur in disorders associated with extensive hepatocellular injury, such as acute viral hepatitis, ischemic hepatitis (hypoxic hepatitis, shock liver), and acute drug- or toxin-induced liver injury (eg, acetaminophen toxicity). (See 'Serum aminotransferases' above.)

- A variety of other hepatic enzymes (such as lactate dehydrogenase) have been measured, but none is as useful as the aminotransferases for the diagnosis of hepatic disease. (See 'Serum concentrations of other hepatic enzymes' above.)

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GRAPHICS

Child-Pugh classification of severity of cirrhosis

Parameter	Points assigned		
	1	2	3
Ascites	Absent	Slight	Moderate
Bilirubin	<2 mg/dL (<34.2 micromol/L)	2 to 3 mg/dL (34.2 to 51.3 micromol/L)	>3 mg/dL (>51.3 micromol/L)
Albumin	>3.5 g/dL (35 g/L)	2.8 to 3.5 g/dL (28 to 35 g/L)	<2.8 g/dL (<28 g/L)
Prothrombin time (seconds over control) or	<4	4 to 6	>6
INR	<1.7	1.7 to 2.3	>2.3
Encephalopathy	None	Grade 1 to 2	Grade 3 to 4

Modified Child-Pugh classification of the severity of liver disease according to the degree of ascites, the serum concentrations of bilirubin and albumin, the prothrombin time, and the degree of encephalopathy. A total Child-Turcotte-Pugh score of 5 to 6 is considered Child-Pugh class A (well-compensated disease), 7 to 9 is class B (significant functional compromise), and 10 to 15 is class C (decompensated disease). These classes correlate with one- and two-year patient survival: class A: 100 and 85%; class B: 80 and 60%; and class C: 45 and 35%.

INR: international normalized ratio.

Graphic 78401 Version 15.0

Causes of an elevated serum lactate dehydrogenase level

Cardiac	Myocyte injury ▪ Demand ischemia ▪ Trauma, cardiovascular surgery ▪ Toxins ▪ Infection (myocarditis, rheumatic fever) ▪ Drugs (alcohol, chemotherapy, cocaine, methysergide, carbon monoxide) Hepatic congestion ▪ Heart failure Hemolysis ▪ Prosthetic valves
Central nervous system disorders	▪ Bacterial meningitis ▪ Cerebral hemorrhage ▪ Cerebral venous thrombosis
Drug-induced	▪ Neuroleptic agents (neuroleptic malignant syndrome) ▪ Withdrawal of L-Dopa or dopamine agonist ▪ Serotonin syndrome ▪ Malignant hyperthermia ▪ Recreational drugs ▪ Myopathies (colchicine, antimalarials, cholesterol-lowering drugs, cocaine, alcohol, glucocorticoid)
Endocrine	▪ Hypothyroidism ▪ Acromegaly ▪ Cushing's syndrome ▪ Diabetic muscle infarction
Gastrointestinal	▪ Acute pancreatitis ▪ Intestinal obstruction ▪ Early acute hepatitis ▪ Ischemic hepatitis
Hematologic	Hemolytic anemias ▪ Inherited (spherocytosis, sickle cell disease, deficiency of red blood cell enzymes) ▪ Acquired (microangiopathic hemolytic anemia, PNH, immune hemolysis)

	Ineffective erythropoiesis ▪ Pernicious anemia, folic acid deficiency ▪ Iron deficiency ▪ Primary myelofibrosis
Infection	▪ Pneumocystis pneumonia (late) ▪ Tuberculosis ▪ Malaria ▪ Parasitic ▪ Legionnaires disease ▪ Histoplasmosis ▪ Toxoplasmosis
Malignancy	▪ Leukemias ▪ Lymphomas ▪ Solid tumors (testicular germ cell tumors) ▪ Tumor lysis syndrome (large tumor burden)
Neuromuscular	▪ Myopathies (inherited, acquired, drug) ▪ Periodic paralyses
Pregnancy	▪ Preeclampsia ▪ Adnexal mass in pregnancy ▪ HELLP syndrome
Pulmonary	▪ Pulmonary embolism, infarction ▪ Pulmonary alveolar proteinosis
Renal	▪ Renal infarction
Rheumatologic	▪ Dermatomyositis ▪ MCTD ▪ Rheumatoid arthritis ▪ Scleroderma ▪ Sjögren's syndrome ▪ SLE
Trauma	▪ Rhabdomyolysis ▪ Surgery
Vasculitis	▪ Polyarteritis nodosa ▪ Eosinophilic granulomatosis with polyangiitis (Churg-Strauss vasculitis) ▪ Granulomatosis with polyangiitis [Wegener's]

	▪ Behçet's syndrome ▪ Sarcoidosis
Idiosyncratic LDH elevation	The presence of macro-LDH (LDH combined with an immunoglobulin), not associated with any symptoms or particular disease

PNH: paroxysmal nocturnal hemoglobinuria; HELLP: hemolysis, elevated liver enzymes, low platelets; MCTD: mixed connective tissue disease; SLE: systemic lupus erythematosus; LDH: lactate dehydrogenase.

Graphic 98392 Version 2.0

Contributor Disclosures

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