Liver Function Tests (LFTs)

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ABSTRACT

Each liver function test by itself is neither highly sensitive nor specific but when interpreted together may provide the clinician with useful information about the patient's liver, and may also indicate other health issues such as malnutrition and bone disease.

Keywords: albumin, ALP, ALT, AST, bilirubin, hepatocellular injury, liver function tests

SYNONYMS

Liver Panel, Liver Injury Tests, Liver Profile

TESTS COMMONLY INCLUDED

Liver function tests (LFTs) include alanine aminotransferase (ALT), alkaline phosphatase (ALP), aspartate aminotransferase (AST), bilirubin and albumin.

SPECIMEN

Serum is the specimen of choice. Blood may be collected in serum separator tubes with or without additives.

All specimens should be handled with standard precautions and sent to the lab immediately for processing. Specimens that cannot be analysed immediately should be centrifuged, serum refrigerated and analysed as soon as possible.

INDICATIONS

As the liver is involved in excretory, synthetic and metabolic functions, LFT may be ordered by clinicians as a standard order for non-specific symptoms (such as fever, fatigue, nausea, abdominal pain, muscle pain, joint pain and weight loss) or as part of general health screening for opportunistic discovery of occult disease. Clinicians may also order LFT to confirm their pre-clinical suspicion of specific liver and non-liver diseases. Liver disease may be broadly categorised into 4 groups: inflammatory, vascular, metabolic and neoplastic disorders. Viral infection, hepato-toxic drugs and alcohol abuse cause hepatitis and hepatocyte injury, and hence liver inflammation. Chronic liver inflammation (e.g. hepatitis viruses or haemochromatosis) often leads to cirrhosis; a condition characterised by irreversible liver scarring and fibrosis, and increased risk for liver cancer. Metabolic disorders that affect the liver include the hereditary alpha-1 antitrypsin deficiency, Wilson's disease and haemochromatosis. Cancers in the liver may arise de novo in the liver, progress from cirrhosis or spread from cancers elsewhere.

ALT and AST

ALT and AST are sensitive indicators of hepatocellular injury but they lack specificity as they are also present in muscle (cardiac and skeletal), kidney, and RBCs. In hepatocyte cytoplasm AST is more abundant than ALT. However, in plasma AST is cleared more rapidly (t½ 16-18 hours) than ALT (t½ 42–48 hours). Consequently, the upper reference limit for ALT is higher (55 U/L) than that for ALT (45 U/L). These aminotransferases may be increased in patients presenting with cirrhosis, chronic hepatitis, alcoholic hepatitis, acute viral hepatitis and toxic ischemic injury. Marked increase of the

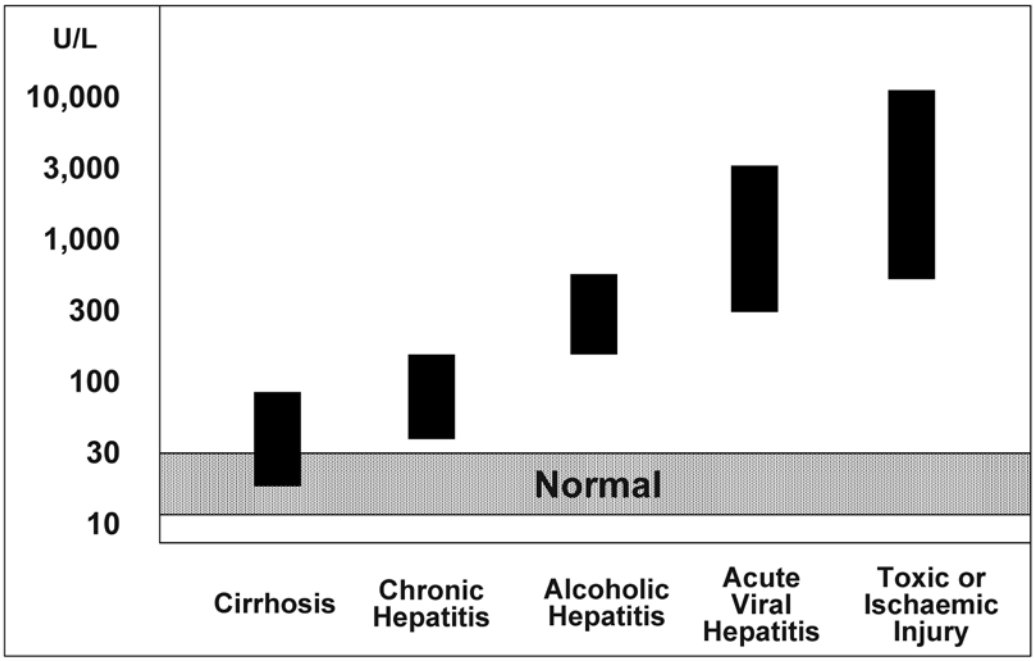

Fig. 1. Typical serum AST or ALT values for various liver conditions.

aminotransferases (>15 times the upper normal) suggests acute hepatitis and hepatoxicity such as acetaminophen overdose. The diagnosis for alcoholic hepatitis is supported by the finding of a ratio of AST to ALT of at least 2:1 and gamma-glutamyl-transpeptidase (GGT) that is twice the normal level[3]. The AST:ALT ratio may also be used to differentiate between different conditions: high ratio in hepatitis C with cirrhosis, liver metastases and HCV with cirrhosis versus low ratio in acute inflammation and cholestasis[4]. The log of aminotransferase range in U/L against normal subjects, and the diagram may be used to guide interpretation of ALT and AST results (Fig. 1.)[5].

ALP

ALP is found in the liver, bone, kidney, intestine and placenta. Serum ALP is thus a mixture of different ALP isoenzymes and can be fractionated by electrophoresis. In normal serum, ALP comprises the liver and bone moieties; bone ALP is heat labile. Liver ALP, found on canalicular surfaces, is raised in any condition of biliary obstruction (intrahepatic and extra-hepatic). In hepatocyte injury, ALP is often normal or marginally elevated. This feature is used as a guide to differentiate liver parenchymal disease from biliary dysfunction. It is unusual to require ALP isoenzyme fractionation for distinguishing bone from liver source of ALP; heat lability is of historic interest only. A bone specific ALP immunoassay (Ostase, Beckman-Coulter) is available but costly and thus not widely used.

Another canalicular enzyme, GGT corroborates the ALP increase in biliary disease. Moreover, GGT is normal in bone disease. Hepatic GGT production is increased with alcohol intake and has been used to indicate alcoholism or alcoholic liver disease. However, GGT is elevated with medications (anticonvulsants and histamine receptor blockers), prostate disease, obesity, diabetic nephropathy and hypertension. Hence, this mitigates against its use as a routine LFT.

Bilirubin

Serum bilirubin is a mixture of α, β, γ and δ fragments which are unconjugated, singly conjugated, doubly conjugated and covalently bound to albumin, respectively. Although δ bilirubin measurement is available, it has not gained wider utility. In most cases a total bilirubin assay suffices for LFT, but fractionation may be required in isolated increases in bilirubin and neonatal jaundice. Direct bilirubin (DB) refers to the conjugated bilirubins that react directly with the diazo reagent, while indirect

bilirubin is a derived value obtained from the difference of the total bilirubin and DB. DB assays measure only 70–90% of the conjugated and δ bilirubins, and may underestimate the severity of jaundice. Direct measures of conjugated and unconjugated bilirubin is available (Vitros BuBc, Johnson & Johnson), but its use is confined to a minority of labs.

Serum bilirubin is useful in separating the causes of jaundice. In prehepatic jaundice due to haemolysis, unconjugated bilirubin is increased with little or no increase in conjugated bilirubin. In hepatic and post-hepatic jaundice, there is increased conjugated and δ bilirubins.

Albumin

Albumin is synthesised in the liver and is an indictor of liver function. However, serum albumin levels change slowly due to the long half life of albumin together with the capacity of the liver to synthesise albumin at twice the health basal rate to compensate for decreased synthetic capacity or albumin losses. Albumin is decreased by trauma, inflammatory conditions and malnutrition.

Limitations of LFTs

The American Gastroenterological Association (AGA) position statement on liver chemistry tests provides guidelines for a rational approach to the interpretation and further diagnostic evaluation of patients with abnormal liver chemistry tests[1]. The AGA has also provided a technical review of the liver chemistry tests[2]. The AGA stresses in both documents that the interpretation of all abnormal liver chemistries must be applied to the clinical context of the patient such as risk factors for disease, symptoms, historical and physical examination findings.

Conditions other than liver disorders may cause abnormal LFTs and results must be interpreted in the clinical context of the patient. AST and ALT are often normal in patients with cirrhosis as they are released into the blood when liver cell membranes are damaged but not necessarily in necrosis (apoptosis) of liver cells as in liver cirrhosis and fibrosis. Another limitation is that abnormal levels of albumin and bilirubins may be obtained only when liver damage is far along.

Falsely elevated ALT and AST levels may occur due to pre-analytical errors such as obtaining the blood sample after an intramuscular injection or a haemolysed blood sample due to a difficult phlebotomy or haemoconcentration from prolonged tourniquet application. The cytosolic ALT and cytosolic and mitochondrial forms of AST are released into the plasma when the red blood cells are damaged. Haemoconcentration will also compromise albumin results.

ADDITIONAL LAB TESTS

Prothrombin time (PT) is a marker of hepatic synthetic function. It is an early indicator of the transition of chronic hepatitis to cirrhosis. PT is also a parameter that is used to compute the MELD score for considering patients with cirrhosis for transplantation. Adjunct clinical lab tests to investigate liver disease include GGT to confirm alcohol abuse; antimitochondrial antibodies to evaluate autoimmune hepatitis; serologic tests to confirm Hepatitis A, B and C; AFP for liver cancer; and iron studies for the investigation of haemochromatosis. However, it must be noted that clinical lab tests do not prove cirrhosis, fibrosis and tumour without imaging and liver biopsy[6]. A new enhanced liver fibrosis (ELF) immunoassay (Advia, Siemens) comprising a mixture of 3 fragments of liver matrix components — hyaluronic acid (HA), N-terminal fragment of procollagen III (P3NP) and tissue inhibitor of matrixmetalloproteinase-1 (TIMP-1) is gaining currency in Europe as a non-invasive marker of liver fibrosis.

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RECOMMENDED READING

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