Liver function tests

Penelope Coates

This article forms part of our 'Tests and results' series for 2011 which aims to provide information about common tests that general practitioners order regularly. It considers areas such as indications, what to tell the patient, what the test can and cannot tell you, and interpretation of results.

Keywords: liver function tests; liver diseases; gastrointestinal diseases

Liver function tests (LFTs) are a panel of blood markers (*Table 1*) used to assess and monitor several diseases. However, they are not all true tests of liver function and abnormalities may not reflect liver disease.

When should LFTs be ordered?

Indications for liver function testing include investigating and monitoring patients with suspected liver disease, at risk patient groups, or monitoring malignancy; and before initiating and monitoring hepatotoxic medications (*Table 2*). There is no cost effectiveness data for the use of LFTs[1,2] and by definition 2.5% of the healthy population may have an abnormal result at any one time, usually mild.

What to tell the patient?

Patients should be aware that a blood test is required. No special preparation, such as fasting, is necessary. Results are often available within 24 hours, although they may be slower in remote areas and may be quicker in urgent situations. Liver function tests attract a Medicare rebate (see *Resources* for a link to a fact sheet for patient information).

What laboratory factors can affect results?

Enzyme gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), aspartate transaminase (AST), and alanine transaminase (ALT) levels involve a monitored reaction and rarely, enzymes may form 'macro' complexes with immunoglobulins or other large molecules, resulting in reduced clearance and a falsely high result. In patients with extremely high enzyme levels, substrate exhaustion may lead to a falsely low result.

To prevent degradation samples should be protected from light if high levels of bilirubin are suspected. Some methods give falsely low results if the specimen is haemolysed.

Serum albumin is routinely measured by dye binding. Different dyes are used – with variable specificity, particularly in the low range, therefore it is preferable to use the same laboratory for repeat tests.

What do the results mean?

It is helpful to classify results as typical of cholestasis (interruption to bile flow between the hepatocyte and the gut) or consistent with hepatocellular damage (*Table 3*).

Raised transaminases (ALT and AST) suggest hepatocellular injury. Marked increases (over 10 times the upper reference limit) suggest an acute or severe insult, for example drugs, acute viral hepatitis or hypoxia. Mildly elevated transaminases (up to five times the upper reference limit) suggest infection, alcohol, fatty liver or medication (*Table 3*). Alcohol often results in a higher AST:ALT ratio than other forms of liver damage. Transaminase levels do not directly correlate to the degree of liver damage, for example in cirrhosis where levels may drop to within the reference range.

Alkaline phosphatase is not specific to the liver, it is also produced in bone, intestine and placenta. A concurrent raised GGT suggests liver origin. Common causes of a raised ALP and GGT are cholestasis and enzyme induction by alcohol or medication.

Isolated raised ALP is typically due to bone disease (eg. Paget disease in patients over

the age of 50 years, vitamin D deficiency, metastasis). On request the laboratory may quantify ALP liver and bone isoforms if the clinical context is unclear and when the total ALP is over 1.5 times the upper reference limit.

Gamma-glutamyl transferase is most useful to confirm the liver origin of ALP. It is associated with alcohol use, although only 70% of isolated raised GGT is due to alcohol excess, and 30% of alcohol abusers will have a normal GGT. Levels remain elevated for 2–3 weeks after cessation of heavy drinking or liver injury.

Bilirubin increases in both cholestatic and hepatotoxic liver disease. In adults, raised bilirubin is usually predominantly conjugated. Unconjugated hyperbilirubinaemia in adults is usually due to Gilbert syndrome or to haemolysis. Gilbert syndrome is a common benign impairment in bilirubin conjugating ability, affecting up to 5% of the population, with a persistent isolated increase in bilirubin up to 2–3 times the upper reference limit. Levels increase during acute illness or fasting and further investigation is unnecessary.

Low albumin can indicate severe liver disease, but is more often from other causes including physiological (eg. pregnancy), inflammation, malnutrition, and protein losing states. Total protein can be useful to estimate the globulin fraction, increased in inflammation. In cirrhosis, low albumin and increased bilirubin are associated with reduced survival.

Table 1. Liver function tests and their site of origin

Bilirubin	Haem metabolite Conjugated in liver
Albumin	Synthesised in liver: half life about 20 days
Total protein	Includes albumin, immunoglobulins and carrier proteins: variable proportion synthesised in liver
GGT	Originates from the canalicular (bile) surface of hepatocyte
ALP	Originates from the canalicular (bile) surface of hepatocyte Also from bone (produced during bone formation), intestine and placenta
AST	Originates from the hepatocyte cytoplasm, hepatocyte mitochondria and from muscle (skeletal and cardiac)
ALT	Originates from the hepatocyte cytoplasm

Table 2. Indications for liver function tests

Indication	Examples
History or examination findings suggest liver disease	• History of poisoning (eg. paracetamol) • Jaundice on examination • History of alcohol abuse • Signs of chronic liver disease including ascites • Family history of haemochromatosis
Screening for populations at high risk of blood borne virus infection	• Contact tracing in cases of hepatitis • Indigenous patients • Illicit drug use • Previous transfusion
Significant nonliver disease that may effect liver function	• Malignancies • Hypoxia
Monitoring medications	• Valproate • Methotrexate

Table 3. Classification of liver function test abnormalities

Pattern	Laboratory features	Common causes
Cholestasis	ALP >200 IU/L ALP more than three times ALT	• Biliary obstruction • Pregnancy (needs further assessment) • Drugs (eg. erythromycin, oestrogen) • Infiltration (eg. malignancy)
Hepatocellular damage	ALT >200 IU/L ALT more than three times ALP	• Infection (eg. hepatitis B, C, A; EBV; CMV) • Alcohol (AST often >2 times ALT) • Fatty liver • Drugs (eg. paracetamol*) • Metal overload (eg. hereditary haemochromatosis, copper overload) • Hypoxia (LD usually >1.5 times AST) • Autoimmune

* Patients with pre-existing liver disease, including alcohol abuse, are vulnerable to paracetamol toxicity even at a standard dose[5]

When should I repeat LFTs and what constitutes a change?

Interpretation and follow up vary with clinical context and results. In selected settings, isolated, unexpected minor abnormalities may be repeated within a short time frame (eg. 1 week.) Almost a third of results will return to the normal range on repeat testing[3] and obviously a persistent abnormality is more likely to be due to significant pathology.

Monitoring patients with existing liver disease or hepatotoxic effects of medications should be done no more often than monthly if the patient is otherwise stable. Three monthly testing is appropriate for some medications (eg. methotrexate).

Daily testing may be appropriate for very acute toxic or hypoxic insult, although twice weekly is more common.

Transaminases ALT and AST have large normal within-subject variability such that serial results are only significant if they differ by more than 30%. Similarly, a significant change for GGT is more than 20%, ALP more than 15%, and bilirubin more than 40%. Albumin has very low intraindividual variation.

Next steps?

Follow up investigations are certainly recommended for patients with severe or persistent abnormalities, or with relevant clinical findings. These investigations are context specific. However, in a hepatotoxic picture investigations such as hepatitis serology, ferritin and transferrin saturation are first line. Further investigation may include tests for less common causes such as copper overload and autoimmune liver disease. In contrast, for cholestatic results the initial emphasis is usually on hepatic imaging with ultrasound.

Case study 1

A woman, 35 years of age, complained of abdominal pain and dark urine. She was clinically mildly jaundiced. Her liver function tests were as follows:

Albumin	36 g/L (34–48)
Protein	83 g/L (65–85)
Total bilirubin	45 µmol/L (2–24)
GGT	439 U/L (<60)
ALP	285 U/L (30–110)
ALT	49 U/L (<55)
AST	43 U/L (<45)

The raised ALP relative to ALT suggests cholestasis and the high GGT confirms liver origin. The mild hyperbilirubinaemia confirms the clinical impression of jaundice. Biliary disease is highly likely with gallstones the most likely differential diagnosis. However, this clinical picture may also occur in drug reactions or infiltrative conditions. After a careful history, abdominal ultrasound is the most appropriate next investigation.

Case study 2

A man, 39 years of age, had the following results as part of an insurance medical:

Albumin	37 g/L (34–48)
Protein	72 g/L (65–85)
Total bilirubin	13 µmol/L (2–24)
GGT	46 U/L (<60)
ALP	81 U/L (30–110)
ALT	76 U/L (<55)
AST	44 U/L (<45)

Mild elevation in transaminases is not an uncommon incidental finding in asymptomatic patients. The commonest causes include chronic hepatitis C infection (affecting up to 3% of the population),[3] fatty liver, and hereditary haemochromatosis. All patients with mildly elevated transaminases should be asked about risk factors for blood borne infections, and should have serological testing for hepatitis C and B. Alcohol use should be reviewed as alcoholic hepatitis and nonalcoholic steatohepatitis have almost identical biochemical and clinical presentations. There is no biochemical test to reliably identify or exclude alcohol abuse. Overweight and obesity increase the risk of fatty liver by six-fold but need not be present to make the diagnosis. Ultrasound shows a bright hyperechoic liver texture, as typically seen in fatty liver. Hereditary haemochromatosis has a frequency of 1:150 in Australia.[4] Only 28% of men and 1% of women homozygous for the most common HFE gene mutation will become overloaded, hence initial screening with fasting iron studies for ferritin and transferrin saturation is recommended.

Case study 3

A man, 66 years of age, presented with weight loss and fatigue. He had a normocytic anaemia. His LFTs were as follows:

Albumin	22 g/L (34–48)
Protein	59 g/L (65–85)
Total bilirubin	12 µmol/L (2–24)
GGT	926 U/L (<60)
ALP	527 U/L(30–110)
ALT	104 U/L (<55)
AST	96 U/L (<45)

The raised ALP relative to ALT again suggests cholestasis, but this time in the absence of jaundice. While medications may be responsible, patient's age, significant symptoms and low albumin (biochemical evidence of severe concurrent illness) suggest intrahepatic cholestasis from liver metastases as a likely cause. It would be unusual for this to be the first indication of neoplastic disease. Again, as in many cases of cholestasis, ultrasound is an appropriate next investigation.

Resources

- The Royal College of Pathologists of Australasia Manual of Pathology Tests – lists clinical problems and individual tests for the clinician. Available at www.rcpamanual.edu.au
- Lab Tests Online – a patient focused site that explains individual tests. Available at www.labtestsonline.org.au
- A useful patient handout is available at: www.patient.co.uk/health/Blood-Test-Liver-Function-Tests.htm.

Author

Penelope Coates MBBS, FRACP, FRCPA, is Clinical Director, Chemical Pathology, Institute of Medical and Veterinary Science, Adelaide, South Australia. penelope.coates@health.sa.gov.au.

Conflict of interest: none declared.

References

1 American Gastroenterological Association position statement: evaluation of liver chemistry tests. Gastroenterology 2002;123:1364–6.
2. AGA Technical review on the evaluation of liver chemistry tests. Gastroenterology 2002;123:1367–84.
3. Lazo M, Selvin E, Clark JM. Clinical implications of short-term variability in liver function test results. Ann Intern Med 2008;148:348–52.
4. Allen KJ, Gurrin LC, Constantine CC, et al. Iron-overload-related disease in HFE hereditary hemochromatosis. N Engl J Med 2008;358:221–30.
5. Zimmerman HJ, Maddrey WC. Acetaminophen (paracetamol) hepatotoxicity with regular intake of alcohol: analysis of instances of therapeutic misadventure. Hepatology 1995;22:767–73.

correspondence **afp@racgp.org.au**