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Liver Chemistries

Liver Function Tests - A Misnomer

The term "liver function tests" is a misnomer as many of the tests do not comment on the function of the liver but rather pinpoint the source of the damage and are in fact indirect markers of hepatobiliary disease or liver injury. Since they are not true measures of hepatic function, they are best referred to as "liver chemistries" or "liver blood tests". True tests of liver function are not commonly performed but include prothrombin time, its ability to produce albumin as well as vitamin K dependent clotting factors and others that are not commonly performed, such as measurement of hepatic substrates that are cleared by hepatic uptake, metabolism, or both processes.

Classification of Liver Chemistries

A. **Tests of the liver's capacity to transport organic anions and to metabolize drugs:** Serum bilirubin, urine bilirubin, urobilinogen etc.

B. **Tests of the liver's biosynthetic capacity:** Serum proteins, albumin, prealbumin, serum ceruloplasmin, procollagen III peptide, a 1 antitrypsin, a feto protein, prothrombin time etc.

C. **Tests that detect injury to hepatocytes (serum enzyme tests):** Aminotransferases (ALT and AST), alkaline phosphatase, gamma glutamyl transpeptidase, 5 nucleotidase, leucine aminopeptidase etc.

a. **Hepatocellular pattern:** Elevated aminotransferases out of proportion to alkaline phosphatase
ALT-predominant: Acute or chronic viral hepatitis, steatohepatitis, acute Budd-Chiari syndrome, ischemic hepatitis, autoimmune, hemochromatosis, medications/toxins, autoimmune, alpha1-antitrypsin deficiency, Wilson disease, Celiac disease
AST-predominant: EtOH-related, steatohepatitis, cirrhosis, non-hepatic (hemolysis, myopathy, thyroid disease, exercise)

b. **Cholestatic pattern:** elevated alkaline phosphatase + GGT + bilirubin out of proportion to AST and ALT
Hepatobiliary causes: Bile duct obstruction, primary biliary cirrhosis, primary sclerosing cholangitis, medication-induced, infiltrating diseases of the liver (sarcoidosis, amyloidosis, lymphoma, among others), cystic fibrosis, hepatic metastasis, cholestasis
Non-Hepatic causes of elevated alkaline phosphatase: Bone disease, pregnancy, chronic renal failure, lymphoma or other malignancies, congestive heart failure, childhood growth, infection or inflammation

c. **Mixed pattern:** Mixed pattern of injury is defined as elevation of both alkaline phosphatase and aminotransferases.

The "R ratio" has been proposed to assess whether the pattern of liver injury is hepatocellular, cholestatic, or mixed. The ratio is calculated using this formula:

R = (ALT value ÷ ALT upper limit of normal [ULN]) ÷ (alkaline phosphatase value ÷ alkaline phosphatase ULN)

R ratio >5: hepatocellular injury
R ratio <2: cholestatic injury
R ratio 2 to 5: mixed pattern

Uses of Liver Chemistries

Screening Non-invasive yet sensitive screening modality for liver dysfunction

Pattern of disease Helpful in differentiating between acute viral hepatitis and various cholestatic disorders and chronic liver disease (CLD)

Assess severity and predict the outcome of certain diseases like primary biliary cirrhosis

Follow up of certain liver diseases and also helpful in evaluating response to therapy like autoimmune hepatitis

Limitations of Liver Chemistries

Lack sensitivity: The LFT may be normal in certain liver diseases like cirrhosis, non cirrhotic portal fibrosis, congenital hepatic fibrosis, etc

Lack specificity: They are not specific for any particular disease. Serum albumin may be decreased in chronic disease and also in nephritic syndrome. Aminotransferases may be raised in cardiac diseases and hepatic diseases.

Assessment of Liver Abnormalities

Elevated LFTs are found in approximately 8% of the general population. These elevations may be transient in patients without symptoms with up to 30% elevations resolving after 3 weeks. Except for serum bile acids the LFT are not specific for liver diseases and all the parameters may be elevated for pathological processes outside the liver. Thus, it is important to view them keeping the clinical profile of the patient in mind.

Clinical assessment: A detailed history should be taken and full physical examination performed with a particular emphasis on alcohol consumption, medications, occupational exposure to toxins, risk factors for viral hepatitis viz. intravenous drug use, sexual promiscuity, homosexual relations, tattoos, non-sterile ear or body piercing, blood or blood product transfusions etc. along with other factors such as diabetes, obesity and hyperlipidaemia in non-alcoholic fatty liver disease, and family history for Wilson's disease, haemochromatosis, autoimmune disease.

Constituents of Liver Chemistries

Bilirubin The most common cause of an isolated elevated bilirubin concentration is Gilbert's syndrome. Most laboratories will routinely report total bilirubin, which comprises unconjugated and conjugated fractions. Unconjugated hyperbilirubinaemia is usually due to haemolysis or impaired conjugation whereas conjugated hyperbilirubinaemia is typically due to parenchymal liver disease or obstruction of the biliary system. In the neonatal period, there may be a physiological increase in total bilirubin, which is unconjugated. This may be pathological if high or prolonged.

Albumin As albumin is only produced by the liver, the serum albumin concentration is often considered as a marker of the synthetic function of the liver. However, over interpretation of the measured concentrations of albumin as a marker of the severity of liver disease is not always merited. Albumin concentrations are reduced in many clinical situations, including sepsis, systemic inflammatory disorders, nephrotic syndrome, malabsorption and gastrointestinal protein loss.

Prothrombin time (PT) and International Normalized Ratio (INR) are assessments of blood clotting, which are used to measure liver

function, as the underlying protein clotting factors (II, V, VII, IX and X) are made in the liver. While a prolonged PT/INR can indicate either acute or chronic liver dysfunction it can also be caused by vitamin K deficiency as seen in fat malabsorption and chronic cholestasis.

Platelets A reduction in platelets, termed thrombocytopenia, is the most common haematological abnormality found in patients with chronic liver disease and is an indicator of advanced disease. Multiple factors culminate in a low platelet count: decreased production, splenic sequestration and increased destruction. Decreased production is a consequence of bone marrow suppression, as caused by alcohol, iron overload, drugs and viridae, and also by a reduction in thrombopoietin levels in chronic liver injury. Splenic sequestration results from hypersplenism, which is a consequence of portal hypertension seen in advanced liver fibrosis. Platelet destruction is also increased non-specifically in liver cirrhosis owing to shear stress, fibrinolysis and bacterial translocation, whereas in specific causes of autoimmune liver disease, immunologically mediated destruction of platelets occurs owing to antiplatelet immunoglobulin.

Alkaline phosphatase (ALP) levels are physiologically higher in childhood, associated with bone growth, and in pregnancy due to placental production. Pathologically increased levels occur mainly in bone disease (eg, metastatic bone disease and bone fractures) and cholestatic liver disease viz. primary biliary cholangitis, primary sclerosing cholangitis, common bile duct obstruction, intrahepatic duct obstruction (metastases) and drug-induced cholestasis. Furthermore, hepatic congestion secondary to right-sided heart failure can also lead to cholestasis (elevated ALP levels and/or bilirubin).

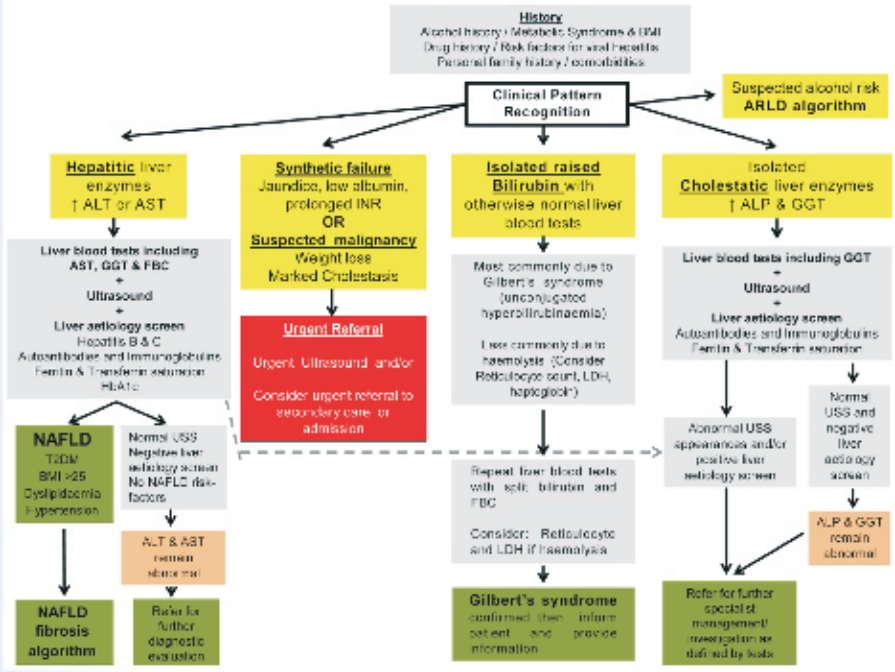
When ALP is elevated in isolation, the measurement of γ-glutamyltransferase can indicate whether the ALP is of hepatic or non-hepatic origin. The most common cause of isolated raised ALP is likely to be vitamin D deficiency. Other causes include Paget's disease and bony metastases. If doubt still exists, the use of electrophoresis to separate the isoenzymes of ALP can differentiate hepatic from non-hepatic causes of increased ALP.

AST and ALT Both enzymes are present in many differing types of tissue, but ALT is considered more liver-specific since it is present in low concentrations in non-hepatic tissue, and non-liver related elevations are uncommon. However, AST is abundantly present in skeletal, cardiac and smooth muscle and so may be elevated in patients with myocardial infarction or myositis. Although ALT is considered a more specific indicator of liver disease, the concentration of AST may be a more sensitive indicator of liver injury in conditions such as alcohol-related liver disease and in some cases of autoimmune hepatitis. In children, creatine kinase measurement may help to determine whether an isolated rise in ALT or AST is due to an underlying skeletal muscle disorder, such as muscular dystrophy.

γ-Glutamyltransferase (GGT) is abundant in the liver and also present in the kidney, intestine, prostate and pancreas but not in bone; therefore it can be useful in confirming that an elevated ALP is of liver and not bony origin. GGT is most commonly elevated as a result of obesity, excess alcohol consumption or may be induced by drugs. Although an elevated GGT has a low specificity for liver disease, it is one of the best predictors of liver mortality. It is particularly useful in children to establish the likelihood of biliary disease when ALP is not a reliable indicator. Predominant causes of cholestasis in children include congenital abnormalities of the biliary tract and genetic disorders affecting bile synthesis and excretion.

Conclusions

1. Abnormal liver tests may present in an asymptomatic patient.
2. A good clinical history and physical examination are often rewarding.
3. Liver tests often become abnormal in non-hepatic diseases.
4. If a systematic approach is adopted the cause is often apparent.



Tests Offered at SRL

Test Name	Method	Test Code
LIVER PROFILE [AST (SGOT), ALT (SGPT), Alkaline Phosphatase, Bilirubin Total & Direct, GGT, LDH, albumin, Globulin, A:G Ratio, Serum Protein Total]	Biochemistry	1388
LIVER PROFILE (without GGT) [AST (SGOT), ALT (SGPT), Alkaline Phosphatase, Bilirubin Total & Direct, LDH, albumin, Globulin A:G Ratio, Serum Protein Total]	Biochemistry	1387
LIVER SCREEN [SGPT, SGOT, Total Bilirubin]	Biochemistry	9111
Prothrombin Time	Biochemistry	3892

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