REVIEW ARTICLE

Liver Function Tests: Biochemical Overview for Clinical Correlation

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Abstract

Aim and objective: To seamlessly integrate the biochemical knowledge and clinical application of liver function tests (LFTs) for easy reference.

Background: The LFTs are one of the key investigations done during patient care. Several times during the patient workup, the complete panel of tests is done which is not necessary and adds extra financial burden on the patients. Medical students and young doctors should be aware of the clear indication of tests, to diagnose the condition and treat it accordingly. Healthcare professionals must use these test results in the proper perspective of patient history and physical examination to arrive at the correct diagnosis.

Conclusion and clinical significance: This article highlights the main parameters tested in LFTs and their interpretation in a convenient and easily accessible format.

Keywords: Biochemical parameters, Clinical biochemistry, Liver function test.

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Background and Introduction

The liver is one of the largest organs and is very important for various functions including metabolism and excretion of toxic and waste compounds from the body.[1] All the compounds ingested are under the control of the liver for their safety and flow into the systemic circulation.[2]

The liver is one of the most heterogeneous organs, both functionally and structurally complex after the brain. The liver is involved in almost all vital metabolic functions including the uptake, metabolism, and excretion of carbohydrates, proteins, fats, cholesterol, fat-soluble vitamins, etc.[3–6]

During embryological development, the ventral foregut endoderm gives rise to the liver.[7] The liver weighs roughly 1.5 kg which is around 2.5% of adult body weight.[8] Histologically, the basic functional unit of the liver is the lobule which is hexagonal in shape with a hepatic venules centrally (also known as a central vein) surrounded by about 4–6 portal areas.[2] This uniform arrangement is referred to as an "isotropic parenchyma".[9]

Previously, the liver has been divided into right, left, quadrate, and caudate segments, but a recent update has suggested that the liver can be subdivided into nine segments based on the vascular and ductal branching patterns. Clinically, it is important to know this compartmental pattern to understand lobar or intralobar deterioration related to interruption of the blood supply and to enable any surgical procedure if necessary.[10,11]

At any given period of time, the liver contains blood equal to almost 25% of the cardiac output. The liver receives blood from the portal vein and the hepatic artery. The portal vein supplies about 70% of the blood flow and 40% of the oxygen while the hepatic artery supplies 30% of the flow and 60% of the oxygen.[6] The liver has numerous types of cells with varying functions as shown in Table 1 along with the extracellular matrix (ECM) which has the following components, matrix metalloproteinases; the glycoproteins laminin, fibronectin, vitronectin, undulin, nidogen (entactin); and proteoglycans such as heparan sulfate.[6,11] This is important in the regulation and adjustment of hepatic function as 5–10% of the liver is collagen.

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The other cells present are the lymphocytes (pit cells); progenitor cells—hepatoblasts; fibroblasts; mesothelia; nerves (unmyelinated); neuroendocrine cells; smooth muscle cells in blood vessels; hematopoietic cells and blood cells (erythrocytes, leukocytes, etc.)

Important Aspects of Hepatocytes

Hepatocytes are divided into three zones which have different key enzymes of metabolic pathways, a pattern known as "metabolic zonation".[24] The zonation preserves the body homeostasis as many opposing pathways are separated to avoid rivalry for the substrate. It is also important to know that zonation is dynamic and changes with response to nutrition, drugs, hormones, and other factors. One such example was glutamine synthase once considered as an example for static zonation, but recent finding shows the response outside the zonation area to thyroid hormones.[25,26]

The following are the zones with their importance;

Zone I is a periportal region and it is well perfused and regenerates fast due to the availability of oxygenated blood with

Table 1: Liver cells and their functions

No	*Liver cells*	*Functions and clinical importance*
1	Hepatocytes (60% of cells and 80% of volume of parenchyma)	Known as workhorses of the liver and have all the equipment to carry out vital functions.
		Involve in the metabolism of energy sources and synthesizes the serum proteins and coagulation factors.[12]
		Detoxify and excrete cholesterol as bile (average about 15 mL/kg/day).[4]
		Involve in steroid hormone and xenobiotic metabolism using mono-oxidases.[13]
		Clinical point:
		As the age increases the number of hepatocytes diminish with hypertrophy and increased polyploidy, lysosomes, and smooth endoplasmic reticulum.[4]
		Whereas mitochondria and peroxisomes remain unchanged with age leading to decreased ability of drug metabolism.
2	Biliary epithelial	The epithelium of the biliary tract acts as a lining channel for bile flow and is also effective communicators with surrounding cells. They also produce mediators responding to injury and cell growth.
3	Endothelial sinusoids, arteries, veins, and lymphatics	The sinusoidal endothelial cells (SECs) constitute 20% of the liver cells and act as a barrier between blood and hepatocytes to filter fluids, solutes, and particles between the blood and space of Disse.[14,15]
		Clinical importance:
		Fenestrae play an important role in the development of atherosclerosis, cirrhosis, and implantation of tumor metastases.[14,15]
		Smaller fenestrae lead to less cholesterol being removed from blood thereby increasing the risk for atherosclerosis development.
		They can engulf smaller size particles and could play a role in the clearance of viruses.[16]
		In addition, they also function as antigen-presenting cells and secrete cytokines and eicosanoids.[17]
4	Kupffer cells	The liver contains large amounts of Kupffer cells derived from monocytes, which form 15% of the liver cells and are actively phagocytic.[4,11,18]
		They are found within the sinusoids and are in constant activation because of contact with gut-derived particles. When activated, they secrete an immense range of inflammatory mediators such as cytokines, reactive oxygen species, eicosanoids, and nitric oxide.[17]
		Kupffer cells also contain high levels of peroxidase, acid phosphatase, glucose 6-phosphate dehydrogenase.[19]
5	Hepatic stellate cells—HSC (Ito or fat-storing cells)	Constitute around 5% of cells and plays a major role in regeneration, fibrogenesis, and disease such as cirrhosis.[20–23]
		HSC normally produces an extracellular matrix. They also control microvascular tone, store, and process vitamin A and lipid. They can be activated to myofibroblasts capable of producing desmin and smooth muscle actin filaments.

nutrients. It performs a vital role in oxidative metabolisms such as beta-oxidation of fatty acids, synthesis of glucose from non-carbohydrate sources (gluconeogenesis), bile and cholesterol synthesis, and amino acid breakdown.

Zone II is demarcated as the pericentral region of the hepatocytes and zone II sits between zones I and III.

Zone III has the poorest perfusion since it is furthermost from the portal triad. It performs the functions of detoxification and biotransformation of drugs, ketone body formation, glycolysis (breakdown of glucose), lipogenesis, glycogen synthesis for storage, and glutamine synthesis.[27]

Liver Function Tests

The assessment of liver enzymes is one of the routine investigations done to know the status of the liver in various conditions. The various parameters indicate the different conditions the patient may be suffering. A clear knowledge of liver function tests (LFTs) will save time for the physician to treat. The LFT can be used to diagnose a condition, know the progress of disease and monitor the response to treatment. Basically, the liver disorder can be categorized as prehepatic, hepatic, and post-hepatic conditions.

Prehepatic Condition

This encompasses any conditions which put more workload on the liver. The liver is functioning normally, i.e., no abnormality, but the disease process lies proximal to the liver.

Example: Red blood cells (RBCs) breakdown leads to the formation of bilirubin which is normally conjugated by the liver for its excretion. If the patient suffers from any condition leading to

abnormal hemolysis, it will produce more bilirubin and the liver has to do extra work.

Conditions: Malaria, hemolytic anemia, Gilbert's syndrome (decreased hepatic uptake, exacerbated by fasting), Crigler–Najjar syndrome (decreased conjugation), drug-induced, ineffective erythropoiesis, blood transfusion, etc.

Hepatic Condition

Here, the disease process is in the liver itself. The liver abnormity leads to an inability to conjugate the bilirubin. This also leads increase in certain enzymes in blood circulation which can aid in diagnosis.

Conditions: Alcoholic liver disease, hepatitis of various etiologies including Iatrogenic, hereditary hemochromatosis, autoimmune hepatitis, primary biliary cirrhosis or primary sclerosing cholangitis, hepatocellular carcinoma, etc.

Post-hepatic condition

Here, the disease process happens distal to the liver, i.e., obstruction to the biliary tract. This also leads to an increase in various enzymes lining the biliary canaliculi. Conditions: Biliary obstruction due to impacted stones, gallbladder stones, pancreatic tumor, drug-induced cholestasis, etc.

The LFTs can be broadly divided into:

Tests to Detect Hepatic Injury

Measurement of bilirubin, serum bilirubin total, unconjugated bilirubin, conjugated bilirubin, urinary bilirubin, urinary urobilinogen, and specific enzymes.

Tests to Assess Hepatic Function

Serum albumin levels, prothrombin time (PT), etc.

The location and elevation of AST and ALT have significance with regard to various liver disorders. As mentioned the AST has mitochondrial and cytoplasmic fractions, the latter contributing to most of circulating serum AST.[30] Conversely, ALT is found only in cytoplasm and specific to liver tissue. This makes an elevated ALT more specific for hepatocellular injury than AST apart from myopathy diseases.[31] The outline of some parameters of liver function tests have been depicted in Table 2 with their clinical importances.

Discussion

The LFTs are one of the key investigations done during patient care. Medical students and young doctors should be aware of clear indications of tests, to diagnose the condition and treat it accordingly. The LFTs are easy to interpret with a proper understanding of parameters and its uses.

The term LFT is a misnomer as these tests determine liver injury rather than hepatobiliary function. These tests may also indicate other organ injuries. This does not rule out the use of these tests in clinical practice as the combination of patient history, examination, and tests form the triad for accurate diagnosis.

Many times the LFTs are ordered for non-specific symptoms with the likelihood of minimal or no link with liver disease. This will add up the unnecessary financial burden to the patient care.[32] This also corroborated with studies suggesting that many patients referred to hospitals with LFTs did not have significant evidence of liver problems.[33]

Most patients are diagnosed after developing complications such as liver failure or portal hypertension. In this late/pre-terminal stage, the tests such as bilirubin, albumin, and platelet count may be obviously abnormal. Studies have suggested that in necroinflammatory hepatitis diseases liver enzymes are elevated,[34,35] and in apoptotic diseases liver enzymes may be normal or elevated, but the amount of deviation is not related to the stage of progression from simple fatty liver to cirrhosis.[36]

The type of bilirubin increase may not give us the exact etiology but supports the probable diagnosis. The rise of unconjugated bilirubin should be looked into the following differential diagnosis of increased hemolysis, decreased conjugation, severe hepatocellular damage, and hepatobiliary obstruction in later stages.

Abnormal liver enzyme levels may signal liver damage or alteration in bile flow. There will be an isolated abnormality in parameters discussed even in healthy patients and leads to challenges to physicians and may lead to performing costlier tests which may prove unnecessary.[37]

The hepatocellular injury is always confirmed by the raise of enzymes along with other parameters. The release of enzymes is due to altered cell membrane permeability and the concentration of enzymes in hepatocytes zones will indicate the exact site of damage. The viral and autoimmune hepatitis involves the periportal hepatocytes, which have more ALT. The ischemic and toxic damage to the liver involves the central zone which has more AST. That is why we need to use AST/ALT ratio, also known as the De Ritis ratio in evaluating the various liver diseases.[38]

The toxic levels of acetaminophen lead to saturation of sulfate and glucuronide metabolic pathways and pushes more acetaminophen metabolism toward the cytochrome P450 pathway that results in the formation of the toxic metabolite *N*-acetyl-p-benzoquinoneimine (NAPQ1). The study also showed acute liver failure is more common in chronic alcohol abusers and caution must be taken while treating such patients.[39]

In these patients, cytochrome P-450, principally cytochrome CYP2E1, metabolizes acetaminophen into a toxic metabolite, which is detoxified by glutathione. In the case of alcoholics, activation of CYP2E1 for the detoxification of ethanol also metabolizes acetaminophen into its toxic metabolites.[40]

In alcoholic hepatitis, AST is higher than ALT. It should be noted that high AST/ALT in acute hepatitis (>1.5) is indicative of a potential fulminant course and a ratio of >1.0 in chronic liver disease indicates advanced fibrosis.[40,41]

Alcohol consumption can lead to a range of liver diseases varying from fatty liver to alcoholic hepatitis to cirrhosis. Studies have suggested that AST/ALT ratio 2–3:1 raises the probable diagnosis of alcoholic liver disease. This can be explained as there is a decrease in plasma pyridoxal 5′-phosphate which affects the ALT activity without affecting the AST activity.[42] Studies have also shown that once alcohol abstinence is observed with adequate nutrition the levels of pyridoxal 5′-phosphate returns to normal and thereby normalizes the ALT level.[43–45]

The rise of the AST/ALT ratio is also seen in cholecystitis following a gallstone impaction in the distal cystic duct or choledocholithiasis apart from alcoholic liver disease. However, the difference is once

Table 2: LFTs and their clinical significance

Parameter	*Function*	*Clinical importance*
Total bilirubin	Measurement of unconjugated and conjugated.	Suggestive of liver disorder.
		It will not provide the exact location of the disease, i.e., prehepatic or hepatic.
Unconjugated bilirubin	Released from RBCs during the breakdown.	Increased level in blood indicates prehepatic conditions.
	Being water-insoluble binds with albumin for its transport to liver for conjugation process.	Being water-insoluble is never excreted in the urine.
Conjugated bilirubin	The liver conjugates the bilirubin to become water-soluble for its excretion with glucuronic acid by the enzyme UDP-glucuronyltransferase (UGT).	Increased levels in blood indicates intrahepatic obstruction, extrahepatic obstruction.
	Normally not seen in blood in high quantities as the process happens in liver cells.	Being water-soluble excreted in urine as urinary bilirubin. A pathogenic feature of obstructive jaundice.
		Note:
		Only conjugated bilirubin indicates obstructive jaundice outside the liver.
		Both conjugated and unconjugated bilirubin increase indicates pathology within the liver.
Urinary urobilinogen	Normally conjugated bilirubin excreted through bile reaches the intestine (duodenum), part of it will be reabsorbed and other parts by the action of intestinal bacteria lead to the formation of stercobilinogen and urobilinogen.	Normally present in urine.
		Increased amount indicates prehepatic condition (+++) or hepatic condition (++).
		Absence in urine indicates obstructive jaundice.
Stercobilinogen	Formed in intestine	Normally present in stools.
		Absence (clay color stools) is a direct indication of obstructive conditions.
Urine bilirubin	Normally absent in urine.	Seen in obstructive conditions of the biliary tract.
		A minimal amount is also seen in hepatic conditions which shows an increase in unconjugated and conjugated bilirubin in the blood.
Enzymes		
Alanine transaminase (ALT)	Belong to aminotransferases or transaminases group of enzymes.	Raised levels indicate hepatocellular injury.
	Produced by hepatocytes and direct indicator of hepatic injury.	
	Also located in other tissues such as the heart, kidney, and skeletal muscle but high in the liver.[28]	
	Levels vary with exercise.	
Aspartate transaminase (AST)	Belong to aminotransferases or transaminases group of enzymes.	Used along with ALT for diagnosing liver damage.
	Two isoenzyme forms.	
	In hepatocytes, it is a mitochondrial enzyme and in skeletal muscle, heart, and kidney it is cytosolic.	
	Released by hepatic cell damage.	
	Non-specific indicator of hepatocellular damage.	
Alkaline phosphatase (ALP)	Produced by cells lining the bile ducts and canaliculi.	Value raised in various conditions other than bile duct diseases, cholestasis, such as bone disease and metastasis, renal condition, physiological during pregnancy, in a growing child, etc.
	There are four isoenzyme forms based on tissue specificity	
	Placental alkaline phosphatase (PLALP) also known as Regan isoenzyme	
	Intestinal alkaline phosphatase (IALP)	
	Germ cell ALP (GCALP)	
	Liver/bone/kidney alkaline phosphatase (L/B/K ALP)[29]	
	Released during cholestasis.	
Gamma-glutamyl transferase (GGT)	Apart from the liver and biliary epithelial cells present in the kidney, pancreas, and intestine.	Raised levels indicate biliary obstruction.

Contd…

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Parameter	*Function*	*Clinical importance*
		Should be used along with ALP as chronic alcoholism increases the levels with hepatic enzyme induction.
		Drugs such as phenytoin, rifampicin increase the levels.
Serum albumin	Synthesized by liver only. Half-life is 21 days.	Decreased levels indicate chronic liver disease.
Prothrombin	Synthesized by liver only.	Prothrombin time increases in acute liver injury.
Serum ceruloplasmin	An acute-phase protein, synthesized by the liver	Raised levels seen physiologically in pregnancy and being an acute phase protein rise seen in infections, rheumatoid arthritis, non-Wilson disease, and obstructive jaundice.
		Low levels are seen in neonates, protein-energy malnutrition (Kwashiorkor and marasmus), protein-losing enteropathy, aceruloplasminemia.
Procollagen iii peptide		Raise seen in hepatic fibrosis, inflammation, and necrosis.
		Need to do serial measurements to follow-up on the chronic liver disease.
Alpha 1 antitrypsin	Is a glycoprotein, synthesized by the liver, a serine proteinase inhibitor.	Raised in inflammatory conditions, pregnancy, and use of oral contraceptive pills.
Alpha-fetoprotein	Seen in early gestation in the fetus at high concentration later decreasing to very low levels.	Raise is characteristic of hepatocellular carcinoma.

the disimpaction of the stone occurs, there is a reversal of this ratio. In advanced hepatic fibrosis, there is a reversal in the AST:ALT ratio in chronic when compared with acute hepatitis.[46]

Studies have suggested that aminotransferases levels vary with various factors such as age, gender, race, and body mass index.[47] The levels will be high in obese, patients on dialysis, African American males and defect in clearance in some populations and losing weight have shown the decline in ALT levels.[48–50]

Occupations like mushroom picking (*Amanita phalloides*) and those involved in the chemical industry (vinyl chloride) could lead to aminotransferase elevation.[51]

In cases of post-obstructive conditions, the most commonly used enzyme assay is alkaline phosphatase (ALP) and must be complemented with gamma GGT. The gamma GGT alone cannot be used for the diagnosis of cholestasis as its diffusely located in the endoplasmic reticulum of bile duct cells. In conjugation with ALP, it indicates the raise of enzymes is specific and not derived from other organ damage.[52]

The rise of unconjugated bilirubin without conjugated bilirubin indicates extrahepatic origin such as hemolysis. Without hemolysis, we can suspect the case of a defect in hepatic cells in terms of conjugation process or excretion. On the other hand, high levels of conjugated bilirubin are suggestive of biliary obstruction with various etiologies. We should also keep in mind the hereditary disorders with defects of secretion, i.e., Dubin-Johnson and Rotor syndrome.

It has been shown that increased total serum bilirubin with prolonged PT have poor outcomes in alcoholic hepatitis patients.[53]

The serum albumin levels indicative of chronic liver diseases, before the increase in bilirubin or prothrombin the decline in albumin levels, indicates advanced liver cirrhosis. It should also be noted that albumin levels decrease in other conditions such as malnutrition, nephrotic syndrome, and chronic infections.

Studies have shown the level of albumin correlates with the prognosis of patients with or without ascites.

The rate of albumin synthesis correlates with the Child-Turcotte or Child-Pugh score.[54]

Hormones such as corticosteroids and thyroid hormone stimulate albumin synthesis by stimulating the concentration of albumin mRNA and tRNA in hepatocytes.[55]

In ascites, there may be a normal synthesis of albumin but the levels may appear reduced because of an increased volume of distribution.[56,57]

The PT is the best indicator of acute injury to liver cells. Apart from factor VIII, all coagulation factors are synthesized by the liver and obviously will have an abnormal coagulation profile in liver diseases. It should be borne in mind that most clotting factors are dependent on vitamin K and deficiency or inhibition of vitamin K alters the PT. The vitamin K deficiency is seen in patients with chronic cholestasis, fat malabsorption conditions.[58]

Prothrombin time serves as a prognostic indicator for acute and chronic hepatocellular disease. In acute hepatocellular disease elongation of PT suggests an increased likelihood of acute hepatic failure. The PT also is a predictor of acetaminophen toxicity, acute alcoholic hepatitis, and poor prognosis in chronic liver disease.[59]

Prolongation of PT is also seen in hypovitaminosis K and parenchymal disease. In the former condition, it returns to normal or improves within 24 hours of single parenteral injection of vitamin K1, whereas in the latter condition it shows only minimal improvement. But patients with an extrahepatic obstruction such as extra hepatic biliary atresia (EHBA) would respond promptly to a single injection of vitamin K1.[60]

Conclusion

This article highlights the importance and relevance of liver function disease in clinical settings. Knowing the different parameters which can be measured and the conditions in which they are altered will help the healthcare professionals in making an accurate diagnosis. This knowledge would also prevent the LFT from being unnecessarily ordered saving both time and money for the patients.

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