ABSTRACT
The liver performs a multitude of tasks in addition to biotransformation of drugs. If a patient is having signs and symptoms of a liver disease, it is vital to assess liver function by performing a liver function test (LFT) as liver diseases require distinct dental management procedures. LFTs measure various liver functions such as metabolic activities and injury to hepatocytes, biosynthetic activities and transport functions. Hence, having knowledge of various measurements of the LFTs is imperative in managing dental patients with liver diseases. This is an attempt to highlight the important aspects of the LFTs for practicing dentists to prepare them in managing patients with liver diseases.

INTRODUCTION
Several enzymes are synthesized by the liver and measurement of these enzymes utilized in several laboratory tests to evaluate liver function. Therefore, knowledge of liver diseases is important for the dental professional due to several reasons. Importantly, hepatic impairment affects metabolism of many dentoally administered drugs including the amide local anesthetics (LAs). Unlike ester LAs such as procaine, benzoicaine and so on which get metabolized in the plasma, amide LAs such as lignocaine undergo metabolism in the liver. Since the liver is the main site of drug biotransformation, all the LAs eventually enter the liver for metabolism and in the event of liver impairment, the LAs gradually accumulate in the circulation which may give rise to LA systemic toxicity (LAST) with manifestations of CNS toxicity\(^1\). Moreover, poor synthesis of clotting factors as a result of liver diseases can affect bleeding tendency. Chronic liver diseases might give rise to excessive bleeding following dental extractions, due to inadequate clotting factors. This necessitates the measurement of the clotting status of the patient\(^2\).

Liver diseases include hepatocellular damage due to hepatitis (e.g. viral hepatitis A, B and C) and toxins, cholestasis or bile duct obstruction due to extra-hepatic (gallstone, cancer) and intra-hepatic factors (drugs), cirrhosis or infiltrative diseases like carcinoma. Signs and symptoms of liver diseases include jaundice (icterus), ascites, gynecomasia (enlargement of breast tissue in males), leukonychia (white nails), palmar erythma, dupuytren's contracture (bending of fingers towards the palm due to palmar fibromatosis), telangiectasis (spider veins), xanthomas (yellow fat plaques underneath the skin), anorexia, weight loss, caput medusa (epigastric veins becoming engorged and superficial), and so on. Therefore, if a patient is having signs and symptoms of a liver disease or has a history of chronic alcohol intake which could lead to a liver disease, it is important to assess liver function by performing a liver function test (LFT). Even patients having diabetes, metabolic syndrome or chronic hepatitis A or B might have altered LFTs.

Hence, manifestations of these symptoms and signs warrant a referral of the patients to their general health care professional and obtaining
a LFT, as liver diseases require distinct dental management procedures. Ideally, interpretation of LFTs should be performed along with the patient’s clinical condition and knowledge of various measurements of LFTs also come in handy when treating dental patients.

Liver Function Tests

Scientifically speaking, the term ‘liver function tests’ is a misnomer since the tests actually do not measure the ‘function’ of the liver as such; rather, they show the amount of liver damage or injury\(^3\). For example, increased levels of enzymes such as serum aminotransferase and alkaline phosphatase are suggestive of liver injury but are not parameters of degree of liver function. Therefore, the term ‘liver biochemical markers’ or ‘liver chemistries’ is more appropriate\(^3\) when discussing the markers such as aforementioned enzymes and levels of bilirubin or protein levels. The liver function test is not a single test. These tests measure various liver functions such as metabolic activities and injury to hepatocytes, biosynthetic activities and transport functions.

Indices That Detect Hepatocellular Injury/Death

1. Aminotransferases

Two aminotransferases (transaminases) namely, aspartate aminotransferase (AST), alanine aminotransferase (ALT) previously known as serum glutamate oxaloacetic transaminase (SGOT) and serum glutamic pyruvate transaminase (SGPT), respectively are commonly used to measure the hepatocellular injury or cell death. ALT is mainly found in the cytosol of the hepatocytes while two isoenzymes of AST are found in the mitochondria of hepatocytes and cytosol of many tissues including the tissues of the heart, skeletal muscle, kidney, brain and liver. Hence, compared to AST, ALT is a more specific marker of liver damage. In healthy persons, liver mitochondrial isoenzyme of AST is accounted for about 80% AST activity whereas AST found in the circulation is due to the cytosolic isoenzyme\(^3\). Though the cytosolic isoenzyme can easily enter the circulation as a result of mild alteration in the cellular permeability, the mitochondrial isoenzyme is released only following damage to the hepatocytes. Hence, an elevated serum AST is an indicator of hepatocyte death due to injury or apoptosis (programmed cell death), as both cytosolic and mitochondrial fractions can contribute to the increase of AST in serum. As AST is localized in other tissues than that of the liver, the damage to skeletal muscles or cardiac tissues also can lead to increased serum AST levels; for instance, elevated AST levels can be observed in acute myocardial infarction\(^5\).

Usually ALT and AST participate in gluconeogenesis. The transfer of an amino group from alanine to \(\alpha\)-ketoglutarate is catalyzed by ALT while AST catalyzes the transfer of an amino group from aspartate to \(\alpha\)-ketoglutarate, giving rise to pyruvate and glutamate and oxaloacetate and glutamate respectively as shown below. The cofactor necessary for these reactions is pyridoxal-phosphate (PLP) which is the active form of vitamin B\(^6\). It has been shown that ALT increases due to the intake of certain drugs and strenuous exercise. Though ALT can be considered a more specific marker for hepatocellular damage, increase of both enzymes occur in injury to liver cells. Therefore in the laboratory, measurement of levels of transaminases is performed by coupling their reaction of formation of pyruvate and oxaloacetate with NADH which gives rise to a change in the intensity which could be read colorimetrically at 340 nm as follows.

AST to ALT Ratio [AST: ALT]

The AST to ALT ratio is useful in the diagnosis of certain condition; for example, AST: ALT more than 2 commonly suggests alcoholic liver disease. Reduced elevation of ALT is probably due to the lack of pyridoxine in alcoholics. In viral hepatitis, the ratio is usually below\(^1\), which gradually increases with the progressive development of cirrhosis. In the case of viral hepatitis, cholestatic hepatitis
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ALT:
Alanine + α-Ketoglutarate → Pyruvate + Glutamate
Pyruvate + NADH + H⁺ → Lactate + NAD⁺

AST:
Aspartate + α-Ketoglutarate → Oxaloacetate + Glutamate
Oxaloacetate + NADH + H⁺ → Malate + NAD⁺

The degree of increase of ALT and AST in serum is suggestive of many liver conditions as given in Table 1

<table>
<thead>
<tr>
<th>Serum Concentration</th>
<th>Liver Condition/Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Alcohol hepatitis, non-alcoholic fatty liver disease, chronic viral hepatitis (hepatitis B and C)</td>
</tr>
<tr>
<td>ALT - 10-55 U/L</td>
<td></td>
</tr>
<tr>
<td>AST - 10-40 U/L</td>
<td></td>
</tr>
<tr>
<td>&lt; 300 IU/mL</td>
<td>Acute viral hepatitis, autoimmune hepatitis, drug induced hepatitis</td>
</tr>
<tr>
<td>500 IU/mL and 5,000 IU/mL</td>
<td></td>
</tr>
<tr>
<td>&gt; 5,000 IU/ml</td>
<td>Acetaminophen related liver failure, severe viral hepatitis, ischemia, circulatory shock or herpes simplex hepatitis</td>
</tr>
</tbody>
</table>

and chronic active hepatitis, the plasma levels of ALT exceeds that of AST.

2. Phosphatase
Alkaline phosphatase (ALP) is a family of isoenzymes responsible for release of phosphate groups (dephosphorylate) from various molecules such as proteins and nucleotides. ALP is found in many tissues including tissues of the liver, bone, placenta, intestine (mucosal epithelia) and kidneys (proximal convoluted tubule). The liver contributes mainly to the serum ALP while about 50% of serum ALP is from bone. In hepatocytes, ALP is localized to the cells lining canaliculi, thus accumulation of ALP occurs consequent to cholestasis which is the commonest cause for elevated ALP (Table 2) Metabolic bone disease such as Paget’s disease causes increased ALP levels without any involvement of the liver. Interestingly, ALP may increase in certain malignant conditions in organs such as the pancreas, independent of the involvement of bone or the liver. These tumour specific isoenzyme are referred to as Regan, Nagao and Kasahara-isoenzymes. The laboratory measurement of ALP is performed by adding p-nitrophenylphosphate as substrate. Colourimetric measurement of formation of p-nitrophenol is done at a wavelength of 405 nm using a spectrophotometer.
3. Transpeptidases

Gamma glutamyl transpeptidase (GGT) is another enzyme found in biliary epithelial cells and hepatocytes. Due to its nonspecific nature of localization in various tissues other than the liver, for example, kidneys, pancreas, intestine and prostate, its usefulness alone is restricted. Nevertheless, serum GGT levels are mainly contributed by hepatobiliary system despite its high concentration in the kidneys. The normal range of GGT is 0–30 IU/L. Elevated levels of GGT have been observed in many clinical conditions such as hepatitis, myocardial infarction, diabetes mellitus (DM), cirrhosis, hepatocellular carcinoma (HCC), chronic obstructive pulmonary disease and so on. It has been shown that though serum GGT is elevated in DM, it does not show any correlation with hepatomegaly. Serum GGT increases in hypertriglyceridemia in diabetes and the level decreases especially when diabetes is treated with insulin. Certain drugs like barbiturates and anti-epileptics such as carbamazepine and phenytoin and alcohol may cause an increase in plasma GGT levels.

4. 5’ Nucleotidase (NTP)

NTP is a ubiquitous protein found in cytoplasmic membranes of cells. NTP catalyzes the hydrolysis of phosphate groups from nucleoside-5-phosphates. The normal serum concentration of NTP ranges between 0–15U/L. Elevated serum levels of NTP are observed in patients having parenchymal liver disease, acute infective hepatitis, chronic hepatitis, hepatic metastases, obstructive jaundice and bone disease. NTP is considered an accurate index in the diagnosis of early onset of primary or secondary tumors of the liver.

Indices to Show the Liver’s Capacity to Metabolize Drugs and Transport Organic Compounds

<table>
<thead>
<tr>
<th>Serum Concentration</th>
<th>Liver Condition/Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>high in children and adolescents and in males compared to females, and in the third trimester of pregnancy</td>
</tr>
<tr>
<td>ALP - 45 to 115 IU/L</td>
<td>hypothyroidism, pernicious anaemia, zinc deficiency and congenital hypophosphatasia</td>
</tr>
<tr>
<td>Low levels of ALP</td>
<td>cirrhosis, hepatitis and congestive cardiac failure</td>
</tr>
<tr>
<td>Mild elevation</td>
<td>both intrahepatic and extrahepatic cholestasis</td>
</tr>
<tr>
<td>ALP (10-12 times of upper limit)</td>
<td>bone diseases such as asphagat’s disease, rickets, osteomlacia, metastatic carcinoma of the bone (osteoblastoma) and hyperparathyroidism</td>
</tr>
<tr>
<td>Drastically high levels of ALP (0-25 times upper limit)</td>
<td></td>
</tr>
</tbody>
</table>
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1. Serum bilirubin

Bilirubin which is a yellow colored pigment, formed as a result of degradation of hemoglobins (Hb) in the red blood cells (RBCs) (95%) as well as degradation of heme-containing enzymes (5%). Bilirubin can be either conjugated (direct) or unconjugated (indirect), and the sum will give the total bilirubin which usually ranges from 0.2 to 1.3 mg/dl (2 to 21µmol/L). Once the haem in the Hb is metabolized into biliverd in in the reticulo endothelial system of the spleen, it is then converted into water-insoluble unconjugated bilirubin (normal range: 0.1 to 0.6 mg/dl or < 12µmol/L) which is then transported to the liver in the circulation by binding to albumin, where it gets conjugated (normal range: 0.1 to 0.4 mg/dl or < 8µmol/L) with glucuronic acid by UDP-glucuronyl transferase making the bilirubin more water soluble and ready to be excreted. Then the conjugated bilirubin enters the small intestine and the bacteria in the intestines breakdown the conjugated bilirubin into bilinogens, out of which, 20% of urobilinogens enter the liver via enterohepatic circulation while a certain amount enters the systemic circulation and gets excreted via the kidneys by glomerular filtration. Usually total and conjugated bilirubin are measured and the difference gives the unconjugated concentration. The Diazo method (Van der Bergh method) is commonly employed to measure serum bilirubin. In this method, diazotized sufanilic acid is added to the patient’s serum which in turn converts bilirubin into azobilirubin (purple in colour). Colorimetric measurement of the color intensity of azobilirubin is then performed at a wavelength of 550 to 580 nm. Since unconjugated bilirubin is not water-soluble and is highly bound to plasma albumin, it is not filtered by glomerulus whereas conjugated water-soluble bilirubin is easily filtered and excreted via urine. Hepatocellular damage giving rise to hyperbilirubinemia also results in excretion of more conjugated bilirubin. In the case of initial stages of viral hepatitis, conjugated bilirubin may be found in the absence of elevated serum bilirubin levels.

2. Urine bilirubin

Since unconjugated bilirubin is not water-soluble and is highly bound to plasma albumin, it is not filtered by glomerulus whereas conjugated water-soluble bilirubin is easily filtered and excreted via urine. Hepatocellular damage giving rise to hyperbilirubinemia also results in excretion of more conjugated bilirubin. In the case of initial stages of viral hepatitis, conjugated bilirubin may be found in the absence of elevated serum bilirubin levels.

3. Urine urobilinogen

Urobilinogen is formed in the intestines as a result of bacterial breakdown of bilirubin which enters the intestine via the biliary tract. The urobilinogen thus formed is absorbed and enters the liver via enterohepatic circulation whereas a certain fraction enters the systemic circulation and is excreted via urine. Thus, a rise in the urobilinogen in the urine indicates hepatocellular injury. Elevated urobilinogen is a good indicator of malignant disease of the liver, liver damage due to alcohol and cirrhosis.
Indices That Demonstrate Synthetic Functions of the Liver

1. Serum albumin
   Measurement of serum albumin concentrations truly reflects the function of the liver. Except immunoglobulins which are synthesized by B cells and plasma cells, almost all the proteins in the serum are synthesized by the liver. The liver parenchymal cell synthesis of proteins include albumin, coagulation factors and fibrinogen and most of the α and β globulins. In the case of albumin, it is exclusively synthesized by the liver thus, any impairment of liver function manifests in changes in levels of albumin. Usually plasma levels of albumin ranges between 3.5 and 5.0g/dL and albumin has a half-life of three weeks (20 days).

   Certain disease conditions like acute viral hepatitis, obstructive jaundice and drug related hepatotoxicity will not change the serum albumin levels whereas in chronic liver conditions like cirrhosis, the serum level of albumin will be lower than 3g/dl. On the other hand, hypoalbuminemia should not be considered a result of only liver disease since certain other diseases like nephrotic syndrome and chronic protein losing enteropathies and even protein malnutrition can give rise to low serum albumin levels.

2. Globulins
   Total globulins include the and globulins synthesized mainly in the liver and globulins synthesized by plasma cells and B lymphocytes. Certain immunoglobulins such as IgG, IgM and IgA are elevated in autoimmune hepatitis, primary biliary cirrhosis and chronic protein losing enteropathies and in alcoholic liver disease, respectively.

3. Serum ceruloplasmin
   Ceruloplasmin, an acute phase protein is important in the transportation of copper in the circulation. Ceruloplasmin is mainly synthesized in the liver and the plasma concentration of a normal adult ranges between 200 and 600mg/L. Elevated levels of ceruloplasmin is observed in many liver conditions such as non-Wilson liver disease and obstructive jaundice as well as in infections and rheumatoid arthritis.

4. Feto protein (AFP)
   Alpha-fetoprotein (AFP) is a serum protein produced by the foetal liver mainly, and to a certain extent by other tissues like the yolk sac and foetal gut and kidneys. The normal adult range of AFP lies between 0 and 15µg/L. Exaggerated levels of AFP (400 - 500µg/L) are observed in hepatocellular carcinoma (HCC), especially in patients with cirrhosis. Elevated concentrations are also found in liver conditions such as chronic hepatitis, acute hepatitis (especially in the regenerative phase) and in hepatic metastasis.

5. Prothrombin time (PT)
   Hemostasis is a complex process involving a number of clotting factors that are activated in a series of sequential steps or cascades, to prevent or stop bleeding. Coagulation cascade includes the intrinsic and extrinsic pathways which are activated in response to injury and when blood leaks from the blood vessel into tissue space, respectively. These two pathways converge and in the common pathway, activated factor X converts prothrombin into thrombin which then converts fibrinogen into long insoluble strands of fibrin thus creating the fibrin clot or plug. The liver exclusively synthesizes all the clotting factors except factor VIII that include fibrinogen (Factor I), prothrombin (Factor II), labile factor (Factor V), stable factor (Factor VII), Christmas factor (Factor IX), Stuart factor (Factor X), and so on. The liver synthesizes the clotting factors in abundance and only a marked reduction due to considerable hepatic damage may cause excessive bleeding. However, prolongation of PT is one of the earliest and sensitive tests of failing liver.

   The prothrombin time denotes whether the extrinsic pathway is intact or not. When
measuring the PT, recombinant tissue factor or other sources of the tissue and calcium and phospholipids are added to the patient’s plasma. This activates the extrinsic pathway (initially, factor VII) which then activates the other clotting factors (V, X and II), ultimately converting prothrombin to thrombin. The normal PT is about 9-15 seconds. Since vitamin K is important for the carboxylation of factors II, VII, IX and X clotting factors, in addition to liver disease, vitamin K deficiency may also prolong the PT. Warfarin prevents the reduction of vitamin K which is necessary for synthesis of aforementioned vitamin K dependent clotting factors, thus acting as an anticoagulant. International Normalized Ratio (INR) is more commonly employed or else used simultaneously with PT to measure the coagulation profile of patients.

INR is usually given as,

\[ \text{INR} = \frac{\text{patient PT}}{\text{mean control PT}} \times \text{ISI} \]

(ISI = international sensitivity index)

Vitamin K deficiency causing prolonged PT is less common unless a patient is severely malnourished or has a history of prolonged antibiotic usage. Nevertheless, in the case of prolonged PT, parenteral administration of vitamin K1 (5-10 mg) is performed to exclude the possibility of vitamin K deficiency (e.g. due to fat malabsorption). If the PT returns to 30%-100% within 24 hrs of administration, then the prolongation of PT is considered most probably due to hypovitaminosis K but not due to intrinsic liver damage. In addition, warfarin overdose also can prolong PT. Similar to vitamin K administration, rapid reversal and normalization of PT can be achieved by administration of FFP or by treating with Prothrombin Complex Concentrates (PCC) if a patient needs to undergo an urgent dental surgical procedure.

Conclusion
Liver biochemical markers show the deregulation of many functions of the liver such as synthesis, biotransformation, and tissue injury to hepatocytes. Dental patients having simultaneous liver diseases can pose problems especially when required to undergo invasive procedures which involve bleeding and also when it comes to prescribing certain drugs commonly used in dentistry. Hence, a better understanding of the so-called ‘liver function tests’ which actually shows liver chemistries, is important in managing patients in the dental clinic.

References


