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Contribution of liver enzymes in diagnosing hepatic diseases: A review

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Abstract

Liver enzymes are crucial clinical biomarkers for diagnosing and managing various liver diseases. The key enzymes include Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Alkaline Phosphatase (ALP), and Gamma-Glutamyltransferase (GGT). These enzymes are released into the bloodstream when liver tissue is damaged, as they are normally contained within liver cells. Elevated levels of these enzymes can indicate liver abnormalities such as hepatitis, cirrhosis, Non-Alcoholic Fatty Liver Disease (NAFLD), and liver cancer. For instance, increased ALT levels can suggest liver damage, while elevated ALP levels might indicate bile duct obstruction or bone disease. Additionally, these enzymes can also reflect systemic conditions like heart failure, pancreatitis, or muscle disorders. Monitoring enzyme levels over time offers valuable insights into disease progression and treatment effectiveness, aiding healthcare providers in developing management strategies. Clinicians can make well-informed decisions by combining enzyme data with clinical history and other diagnostic tests.

Keywords: Alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, gamma-glutamyltransferase, hepatic, non-alcoholic fatty liver disease

Introduction

The liver is a vital component of metabolism and is situated in the right upper quadrant of the body, beneath the diaphragm. It is in charge of producing digestive enzymes, manufacturing proteins, and primary detoxifying different metabolites ^[1]. Additionally, the liver is important for the synthesis and storage of glucose as well as the control of Red Blood Cells (RBCs). Alkaline Phosphatase (ALP), Gamma-Glutamyltransferase (GGT), Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Prothrombin Time (PT), lactate dehydrogenase, total protein, globulins, albumin, conjugated (direct) bilirubin, unconjugated (indirect) bilirubin, and 5'nucleotidase are among the tests for liver function. The elevation pattern can assist in organizing a differential diagnosis, and these tests aid in identifying the location of hepatic damage ^[2]. AST, ALT, and ALP are not included in the most commonly used scores, such as the Child-Pugh score, Child-Pugh score, and Model for End Stage Liver Disease-Na (MELD-Na) score. Instead, INR, bilirubin, and albumin are used in the Child-Pugh score, and INR and bilirubin are used in the MELD-Na score to determine the mortality of cirrhotic patients.

Liver biochemical studies enzymes involved

The most crucial enzymes to take into account include bilirubin, albumin, PT/INR, ALT, AST, ALP, GGT (Gamma-glutamyltransferase), 5'nucleotidase, and lactate dehydrogenase (LDH).

ALT- It is primarily present in hepatocytes and is also present in muscular, cardiac, and renal tissue, albeit at lower concentrations. As a result, it is unique to hepatic damage. When the d. ALT promotes the hepatocyte's production of glutamate and pyruvate, which is crucial for energy production ^[3]. For males, the typical range for ALT is 29-33 IU/L, and for females, it is 19-25 IU/L. Newer research suggests that the present ALT cut off values may need to be lowered in order to increase the test's sensitivity, which has sparked recent discussions over ALT levels. The efficacy of the test may be lowered because it is thought that the current cut-offs were set using patients who might have had underlying subclinical liver diseases. A 2002 retrospective research with 6,835 individuals suggested that earlier studies that defined

normal ALT levels using the 95th or 97.5th percentile were probably biased by undetected hepatitis C and Non-Alcoholic Fatty Liver Disease (NAFLD). It's crucial to understand that reference ranges for labs vary throughout countries and even within the same labs.

AST

Although it is not as minimal as ALT, the enzyme AST is also present in the liver and can also be found in other sites. The main areas of these sites are the brain, kidney, heart, and skeletal muscles. Aspartate metabolism is primarily aided by AST ^[4]. The existence of the enzyme AST in various tissues makes it necessary to exercise caution when analyzing abnormal levels. $AST < 35$ IU/L is the usual range ^[5].

ALP

Additionally, it is a related liver enzyme that is crucial in determining hepatic diseases, which are mainly located in the placenta, hepatobiliary tract, bone, and, to a lesser extent, the body's intestinal tissue. Range of normalcy: 30-120 IU/L. Because of the enhanced osteoblastic activity linked to bone formation, ALP is often higher in children and teenagers ^[6].

GGT

The enzyme known as Gamma Glutamyltransferase (GGT) is present in the kidneys, liver, biliary tract, seminal vesicles, pancreas, and kidneys. In hepatobiliary disorders, its elevation is frequently important when other liver function tests also rise at the same time. Conditions include biliary illness, the use of cytochrome-inducing drugs, and alcohol addiction are known to cause increased GGT levels. The enzyme is essential for the synthesis and metabolism of glutathione in various bodily tissues. Infants' GGT levels are usually 6-8 times greater than those of adults, which vary from 0 to 30 IU/L ^[7].

Nucleotidase

Although this enzyme is present in many tissues, hepatobiliary or cholestatic disorders are primarily associated with its clinical relevance. It is frequently utilized to assist in determining whether a bone-related problem or a hepatobiliary cause is responsible for a high Alkaline Phosphatase (ALP) result. In reactions involving nucleotide hydrolysis, the enzyme is essential. Results of 5'-nucleotidase should be read in conjunction with high serum ALP, as normal levels range from 0.3 to 3.2 Bodansky units ^[8].

LHD

The body has many isoenzymes of this enzyme, one of which is mostly metabolized by Kupffer cells in the liver. Consequently, elevated LDH levels may result from liver damage or illness. This is non-specific, though, and is rarely used to evaluate liver diseases. Though this can vary slightly according on the laboratory, the usual range for LDH is generally 140-280 U/L ^[9].

Markers of liver synthetic function

Of the entire serum protein, albumin makes up between 50% and 60%. It is one of the primary proteins in blood. Because it is generated in the liver, it can be used as a helpful indicator of the liver's synthetic activity. But as albumin is a

negative inflammatory sign, it can also be influenced by other conditions such as protein deficiency, nephrotic syndrome, fluid overload, protein-losing enteropathy, and systemic inflammation. Among its many vital functions are the maintenance of serum oncotic pressure and the facilitation of the blood's transportation of endogenous compounds (like bilirubin) and exogenous substances (like medications) ^[10].

3.5-5 g/dL is the usual range for normal albumin values. The International Normalized Ratio (INR) and Prothrombin Time (PT) both show how the extrinsic route contributes to the coagulation cascade. The synthesis of many clotting factors, such as factors I, II, V, VII, IX, X, XI, and XIII, in addition to protein C, protein S, and antithrombin, is mostly dependent on the liver. Activated partial thromboplastin time (aPTT) is not always as high as PT and INR because aPTT prolongation *in vitro* is hidden by the production of factors such von Willebrand factor and factor VIII in different organs throughout the body. Because pro- and anticoagulant factors are both lacking in cirrhotic patients, PT/INR and aPTT are not valid measures of bleeding risk.

Furthermore, procoagulant activity alone is measured by PT/INR and aPTT; deficiencies in anticoagulant pathways are not taken into consideration. Due to splenic sequestration and decreased thrombopoietin production, patients with cirrhosis or chronic liver illness also frequently develop thrombocytopenia, which increases the risk of bleeding ^[11]. Although bilirubin's conjugation and excretion are intimately linked to the liver's capacity to carry out these functions, bilirubin itself is not a direct indicator of hepatic synthetic function. The end result of heme breakdown is bilirubin, which in the bloodstream first binds to albumin. It is conjugated in the liver and expelled as bile. Direct and indirect hyperbilirubinemia are two classifications for elevated bilirubin levels. Liver excretion problems, such as cholestasis, Dubin-Johnson syndrome, or Rotor syndrome, are usually the source of direct hyperbilirubinemia. On the other hand, hemolysis or intrinsic liver injury might cause indirect hyperbilirubinemia ^[12].

Common conditions associated with abnormal liver enzymes

NAFLD is a prevalent liver condition; a 2016 meta-analysis estimated that the illness affects about 25.24% of the world's population. ^[13] Nonalcoholic Fatty Liver (NAFL) and Nonalcoholic Steatohepatitis (NASH) are associated with a same disease spectrum. In the absence of interventions or alterations to risk factors, NAFL can progress to NASH and ultimately result in liver cirrhosis ^[14]. Although these terms are frequently used synonymously, it is crucial to remember that management is distinct and that a proper evaluation needs to be conducted. The main distinction between the two can be observed in the histology, where NASH exhibits significant inflammation whereas NAFL just exhibits fatty infiltration. Level of AST and ALT are often slightly increased in NASH ($ALT > AST$) and can be normal in NAFL at times. General metabolic risk factors include obesity, dyslipidemia, and diabetes mellitus. NAFL and NASH are diseases of exclusion. ^[14] Liver cirrhosis is a possible outcome of viral hepatitis, particularly infections with hepatitis B and hepatitis C. These infections frequently result in chronic illnesses. An AST: ALT ratio of less than one (average of 0.59 in 1988) was normal for patients with chronic viral hepatitis who did not have liver cirrhosis.

Conversely, an AST: ALT ratio larger than 1 was present in individuals with both liver cirrhosis and chronic viral hepatitis. It was discovered that this difference was noteworthy, emphasizing the significance of keeping an eye on the AST: ALT ratio in cases of chronic viral hepatitis in order to assist detect possible liver cirrhosis^[15]. One cannot exclude out alcohol use. On the other hand, moderate to severe rises in aminotransferase levels are frequently caused by acute viral hepatitis, with ALT usually rising more than AST. Although large elevations in aminotransferase levels can be caused by acute hepatitis C, these levels are often less noticeable than those caused by hepatitis A and B. Unlike bilirubin, aminotransferase levels peak earlier in the acute period and then progressively decline^[16]. Adult cases of acute hepatitis A and B are associated with raised bilirubin levels, which can result in jaundice (which is more common in hepatitis A) and elevated ALP. Hepatitis A does not cause chronic infection, while people with hepatitis B over the age of six have a 10% chance of acquiring chronic hepatitis^[17]. Iron overload is a result of increased iron absorption from defective iron sensing in the gastrointestinal tract in hereditary hemochromatosis, an autosomal recessive condition^[18]. C282Y and H63D are the hemochromatosis (HFE) gene's two most prevalent mutations. This review will only address hemochromatosis connected to HFE, even though there are other types of hemochromatosis as well. Aminotransferases may somewhat rise as a result of hemochromatosis, with ALT being greater than AST. Although liver function tests are typically non-specific in hemochromatosis cases, increased ALP and bilirubin levels may also occur^[18]. It is thought that elevated bilirubin protects the liver from oxidative damage brought on by too much iron. Furthermore, a 2004 study revealed a favorable association between elevated serum iron levels and bilirubin levels^[19]. It is advisable to conduct iron studies, including testing for iron levels, ferritin levels, total iron-binding capacity, and transferrin saturation, if aminotransferase levels are raised without a clear explanation. It could be wise to get a liver biopsy and undergo genetic testing if these results point to a potential iron overload.

Diagnostic tests

Determining if a pattern is cholestatic, hepatocellular, or mixed is critical when assessing aberrant biochemical testing. Ask about medication, herbal remedies, narcotics, and alcohol consumption first. When examining a hepatocellular pattern, begin with serologic testing to rule out autoimmune and viral causes. Next, do a Right Upper Quadrant Ultrasound (RUQ US) to look for signs of fatty liver. Look at less frequent disorders such alpha-1 antitrypsin deficiency or Wilson disease if these tests are ineffective. A liver biopsy may be required if serology and imaging results are unclear and ALT/AST values are still elevated. Tests for gamma-glutamyltransferase (GGT) and 5'-nucleotidase should be performed in response to elevated alkaline phosphatase (ALP) in order to ascertain whether the elevation is hepatobiliary in origin. The RUQ US can be used to detect ductal dilatation or its lack. If ductal dilation is detected, additional testing may involve Magnetic Resonance Cholangiopancreatography (MRCP) or Endoscopic Retrograde Cholangiopancreatography (ERCP); if not, serological tests such as Anti-Mitochondrial Antibody (AMA) testing may be performed. High ALP levels are a hallmark of both extrahepatic and intrahepatic cholestasis.

The goal in treating extrahepatic cholestasis should be to rule out biliary strictures, malignant blockage, and choledocholithiasis. The workup for intrahepatic cholestasis should rule out sickle cell disease, primary sclerosing cholangitis, and primary biliary cholangitis, among other conditions. Other possible causes, such as total parenteral nutrition, drug-induced cholestasis, ischemic cholestasis, or cholestasis of pregnancy, should be taken into consideration when imaging or laboratory data are unable to offer a definitive diagnosis^[20].

Conclusion

Clinicians often deal with elevated liver biochemical markers. These markers, which are used to identify liver damage, can also be elevated as a result of kidney, bone, placenta, or muscle damage. It is essential to comprehend how these indicators behave biochemically under different circumstances. Imaging and other laboratory tests may be used to guide future studies, which may be necessary to determine if the pattern is cholestatic or hepatocellular. When evaluating aberrant liver biochemical patterns, it's important to take into account the severity of the liver test elevation, drugs, and any other current laboratory abnormalities in addition to the existence of symptoms. Unfortunately, sometimes the diagnosis is still ambiguous after more testing, requiring a liver biopsy.

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Conflict of interest

All authors declare that there are no conflicts of interest.

Data availability statement

No data was used for the research described in the article.

Author's contribution

ManojitBysack (MB) participated in the conception of the study. RajenDey (RD) and Soumaditya Das (SD) participated in literature searches and extraction. MB and SD wrote the manuscript for submission to this journal.

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