

# SIGNIFICANCE OF MILDLY ELEVATED LIVER TESTS ON SCREENING BIOCHEMISTRY PROFILES

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## Introduction

The term "liver function tests" generally refers to a group of biochemical tests employed for the detection of liver and/or biliary tract disease.<sup>1-4</sup> Although this term is somewhat of a misnomer, it is firmly entrenched in daily medical language and often referred to in its abbreviated form, "LFTs". Most automated chemistry batteries include the following liver tests: serum albumin, serum total bilirubin, aspartate aminotransferase and alkaline phosphatase. In addition, some clinical laboratories also include serum direct bilirubin, serum globulin, alanine aminotransferase and gamma-glutamyltransferase (GGT). Finally, serum cholesterol and lactate dehydrogenase may nonspecifically reflect the presence of liver disease, but are not typically considered LFTs.

Biochemical tests for liver disease can be divided into those tests that evaluate liver function and those tests that are markers of hepatobiliary disease.<sup>1</sup> Biochemical tests of liver function, i.e., true LFTs, that are readily available in the commercial laboratory include serum bilirubin, serum albumin, and clotting factors, in particular the prothrombin time. The former two tests are included on the routine chemistry battery, while the prothrombin time is performed in the hematology laboratory. Additional measures of true hepatic function that are often used in clinical research and available in some liver centers include galactose elimination, caffeine metabolism and clearance of dyes such as sulfobromophthalein. Another group of biochemical tests are considered markers of hepatobiliary disease rather than true tests of liver function. These marker tests can be divided into those that signify hepatocellular necrosis, such as the aminotransferases; those that detect cholestasis, such as the alkaline phosphatase and GGT; and those that are disease-specific markers, such as viral serology, autoimmune tests and specific blood tests for Wilson's disease, hemochromatosis and alpha-1 antitrypsin deficiency.

There is no uniformly agreed upon definition of what constitutes "mild", "moderate" or "marked" elevation of individual liver enzymes. However, a working definition of these terms for the purposes of this paper is found in Table 1.

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Table 1

Definition of "mild", "moderate" or "marked" elevation of individual liver enzymes.\*

	Mild	Moderate	Marked
AST or ALT	<2-3	2-3 to 20	>20
Alkaline phosphatase	<1.5-2	1.5-2 to 5	>5
GGT	<2-3	2-3 to 10	>10

\* Numbers in table refer to multiples of the upper limits of normal for the individual enzyme, e.g., <2-3 for mild elevation of AST (normal, 0-35 U/L) indicates values ranging from 70 to 105 U/L.

Biochemical screening studies of asymptomatic individuals documents that 1 to 6 percent have abnormal liver tests<sup>2,5,6</sup>, while the prevalence of liver disease in the general population is estimated to be substantially lower at approximately 1 percent.<sup>2</sup> Thus, many more individuals have abnormal LFTs than actually have liver disease. On the other hand, significant liver disease may exist in patients who manifest only mildly elevated liver tests. The dilemma for the insurance practitioner is to determine the significance of mildly elevated liver tests on a screening biochemical profile and distinguish patients with liver disease from those who exhibit false positive elevations of LFTs secondary to diseases of other organs, drug or alcohol use without liver injury, or insignificant liver conditions such as fatty liver. The use of a battery of LFTs obviously increases the sensitivity of a single liver test.<sup>2</sup> It would be unusual for individuals with significant liver disease to have all LFTs entirely normal. The use of a battery of LFTs also improves specificity; the likelihood of liver disease is quite high when more than one LFT is abnormal. The focus of this review, however, will be the interpretation of a mild abnormality of a single LFT, a finding which challenges accurate interpretation. In particular, this review will address isolated mild elevation of the aminotransferase<sup>9</sup>, alkaline phosphatase, GGT and serum bilirubin. In addition, some general concepts regarding screening will be addressed.

## Screening

In routine practice, LFTs may be used for screening, confirmation of suspected hepatobiliary disease, differential diagnosis, prognosis, and monitoring of natural history or response to therapy.<sup>2</sup> Screening refers to the effort to detect disease in unselected populations of asymptomatic individuals. Routine screening with the use of biochemical profiles might be performed on ambulatory care patients as a component of an annual evaluation, on patients as part of preadmission testing

before hospitalization or on applicants for insurance policies. Sensitivity, specificity and predictive accuracy are important concepts to consider in the interpretation of individual liver tests on screening profiles.<sup>7</sup> The predictive accuracy, i.e., the probability that a positive test indicates the presence of disease and a negative test the absence of disease, is a particularly relevant concept which is dependent on the prevalence of the disease. If one assumes that the prevalence of liver disease in the general population is 1 percent and that the sensitivity and specificity of an individual test is 95 percent each, the calculated predictive value of a positive test is 16 percent.<sup>8</sup> Expressed in opposite terms, there is an 84 percent chance of an abnormal test being false positive in this circumstance. As noted above, however, the probability that liver disease is actually present may be increased by employing a profile of LFTs and finding more than one abnormal test.

These considerations have made the implementation of routine biochemical profiles controversial in the setting of ambulatory care screening or preadmission testing.<sup>9</sup> Factors such as laboratory error, artifact, and statistical definition of "normal" values for biochemical tests all serve to confuse the interpretation of the isolated abnormal value. There are many human and mechanical reasons why laboratory errors might occur; this consideration is resolved in clinical practice by simply repeating the assay. Artifacts may occur when other substances present in serum interfere with the assay utilized to perform an individual LFT. For example, an older colorimetric assay used for the measurement of aspartate aminotransferase was falsely elevated during administration of erythromycin.<sup>10</sup> Finally, the very definition of "normal" introduces the potential for false positive results of any test, since the statistical definition of the normal range is usually defined as that range of values which encompasses 95 percent ( $\pm$ two standard deviations from the mean) of presumed normal subjects. This statistical definition therefore segregates potentially 5 percent of normal persons as being abnormal, with 2½ percent of the normal population being above the normal range. These factors have led some to recommend that the routine use of the entire biochemical profile be abandoned for ambulatory care screening and preadmission testing.<sup>9</sup> In particular, Cebul and Beck recommend that the serum albumin, alkaline phosphatase, and aspartate aminotransferase not be utilized in screening because of low diagnostic yield and lack of safe and effective therapy.<sup>9</sup>

With this background in mind, the remainder of this review will address the potential significance of a mild isolated elevation of an aminotransferase, alkaline phosphatase, GGT or serum bilirubin detected on a screening biochemical profile.

### Aminotransferases

The aminotransferases (formerly transaminases) are the most sensitive indicators of hepatocyte integrity. As their names imply, aspartate aminotransferase (AST or SGOT) and alanine aminotransferase (ALT or SGPT) catalyze the transfer of alpha-amino groups from aspartate and alanine, respectively, to alpha-ketoglutarate.<sup>1,3,4</sup> The most sensitive and specific method for assaying AST and ALT couples the formation of oxaloacetate and pyruvate to the oxidation of NADH to NAD, with latter followed spectrophotometrically. AST is found in liver, cardiac muscle, skeletal muscle, kidney, brain, pancreas, lung, leukocytes and erythrocytes, whereas ALT is present in

highest concentration in liver.<sup>1,3,4</sup> AST is present in both mitochondria and cytosol, but ALT is limited to cytosol. The mitochondrial form of AST is immunochemically distinct from the cytosolic molecule, but is not used in routine clinical biochemistry. The normal serum value is composed predominantly of cytosolic AST but includes both varieties. The mechanisms of cellular release and exact source of normal circulating AST and ALT is unknown.

Serum levels of AST and ALT are elevated to some extent in all liver diseases. The highest elevations (1000 U/L) occur in viral hepatitis, drug- or toxin-induced hepatic necrosis, and shock and/or ischemia to the liver. In most other liver diseases, including chronic liver disease (cirrhosis, chronic hepatitis), cholestasis, and neoplasms, serum levels of AST and ALT are usually only mildly or moderately elevated. AST or ALT levels that extend to greater than 1000 U/L secondary to viral or drug-induced diseases typically return to normal over a period of weeks to months, while marked elevations secondary to ischemia may resolve within days. The absolute level of enzyme elevation does not correlate with the extent of hepatocyte damage or prognosis.

Mild to moderate elevations of AST or ALT are seen in alcoholic liver disease, with values greater than 500 U/L being distinctly unusual. In this setting, elevations of aminotransferases are usually accompanied by abnormalities of other tests such as GGT, HDL-cholesterol, erythrocyte mean corpuscular volume and iron.<sup>11</sup> In alcoholic liver disease, the ratio of AST to ALT may be helpful diagnostically.<sup>12</sup> A ratio of more than two is highly suggestive of alcoholic liver disease. Low ratios of AST to ALT have been advocated as a good index of viral hepatitis; however, in general an ALT of greater than 300 U/L is more discriminatory for hepatitis than is the AST/ALT ratio.<sup>1</sup> In the alcoholic patient, mitochondrial damage in hepatocytes seems to be more extensive, and the ALT level is lower because of pyridoxine deficiency which commonly accompanies alcohol abuse. Finally, the AST can be fractionated into mitochondrial and cytosolic components. Mitochondrial AST appears to be especially useful in identifying patients who are alcoholic with or without alcoholic hepatitis.<sup>13</sup> If commercially available, a mitochondrial AST/ALT ratio may be superior to the AST/ALT ratio in identifying chronic alcoholics.<sup>13</sup>

Thorough studies, including liver biopsy, of patients with asymptomatic chronic mild elevations of AST or ALT are limited. In particular, there are no investigations limited to patients with less than twofold, isolated elevation of AST or ALT. In a Scandinavian study by Hultcrantz, et al, 149 patients with moderately elevated AST for greater than six months underwent liver biopsy.<sup>14</sup> These patients had no symptoms, a normal physical examination, and alkaline phosphatase that was normal or elevated less than twofold. The histologic diagnoses were: 1) fatty liver in 63 percent; 2) chronic active hepatitis or chronic persistent hepatitis in 20 percent; and 3) miscellaneous liver diseases in 17 percent. Fatty liver, a benign condition, was associated with high body weight, alcohol intake, hyperlipidemia and diabetes mellitus.

In a recent American study from Bethesda Naval Hospital, Van Ness and Diehl sequentially evaluated 107 patients referred for evaluation of abnormal liver tests greater than 1.5 times the upper limits of normal for more than three months.<sup>15</sup> This

study included a diverse group of patients, many of whom had obvious and advanced liver disease. They compared the clinical diagnoses prebiopsy to the final diagnoses after performance of biopsy. The positive predictive value of the prebiopsy diagnosis ranged from 56 percent for fatty liver to 88 percent for alcoholic liver disease. They found steatosis or steatonecrosis in 19 percent of biopsies.

Other studies have focused on blood donors found to have mildly elevated ALT. Friedman, et al. performed a clinical and biochemical evaluation of 100 asymptomatic blood donors with mild elevation of ALT.<sup>16</sup> The patients in this study did not undergo liver biopsy. Only six participants had physical findings suggesting liver disease, and other liver biochemical tests were normal or near-normal in all participants. ALT elevation occurred only once in one-third of patients completing the seven-month study, while ALT elevations were intermittent or persistent in the remaining two-thirds of patients. Of the two-thirds with intermittent or persistent elevations, most were obese or used alcohol regularly while 20 percent had no apparent cause for elevation other than possible non-A, non-B hepatitis. Other studies have emphasized the apparent presence of fatty liver, often related to obesity, as the explanation of an elevated ALT in asymptomatic blood donors.<sup>17,18</sup> Saxena, et al. also reviewed literature indicating donor-related factors may play an important role in the interpretation of the serum ALT level.<sup>18</sup> The maximal ALT value is reached between 30 and 40 years of age for men and between 50 and 60 years of age in women. Baseline ALT values are higher in males than females. Diets that are rich in calories or sucrose can affect ALT levels significantly. A short burst of strenuous exercise may result in ALT elevation by as much as 41 percent. ALT values may increase more than 50 percent in individuals who are 50 kg above ideal body weight. ALT values are higher in nonwhites than whites. Finally, intraindividual day-to-day variation, age of sample and presence of lipemic serum may influence the ALT level.

The above studies document that fatty liver, with or without nonalcoholic steatohepatitis (NASH), are frequently the cause of mild elevations of AST or ALT (and also alkaline phosphatase and GGT). The prevalence and clinicopathologic features of NASH are just beginning to be recognized.<sup>19,20</sup> NASH most commonly affects obese, diabetic, middle-aged women. It seldom progresses to clinically significant liver disease. AST and ALT are mildly to moderately elevated, while bilirubin, albumin, and prothrombin time are usually normal. Pathologic features of NASH include hepatocellular fat accumulation, Mallory bodies, and perivenular and pericellular fibrosis; however, marked fibrosis or cirrhosis occurs in approximately 40 percent.

Finally, it should be noted that two other studies of unexplained chronic aminotransferase elevations found a higher percentage of patients to have chronic hepatitis or cirrhosis.<sup>21,22</sup> In the study of Hay, et al. from the Mayo Clinic, 47 individuals who had undergone biochemical screening were thoroughly evaluated for the cause of their elevated AST or ALT.<sup>21</sup> Only patients with greater than threefold elevation of AST were included in this study, which found that 51 percent of patients had chronic active hepatitis, many of whom had associated cirrhosis. In the other study from the Cleveland Clinic, 79 patients with an elevated AST found on screening of over 3000 outpatients underwent evaluation.<sup>22</sup> Only five

elevated AST values were not confirmed by abnormalities in additional laboratory tests, and alcoholic liver disease, viral hepatitis, unclassified liver dysfunction, muscle insult and hypothyroidism accounted for the underlying diagnoses.

In summary, mild elevation of aminotransferases (less than 2-3-fold) may be false positive secondary to laboratory error, statistical quirk, or disease of another organ system, or they may often be explained by inconsequential liver disease such as fatty liver. On the other hand, abnormalities of aminotransferases that are greater than twofold, and particularly greater than threefold elevated, or elevations that occur in association with abnormalities of other liver tests are most likely explained by significant underlying liver disease. These conclusions must remain general in nature pending the availability of careful analysis of a large population of patients with isolated mild elevation of aminotransferases.

### Alkaline Phosphatase

Alkaline phosphatase refers to a family of enzymes that hydrolyze a number of phosphate esters at an alkaline pH.<sup>1,3</sup> There are a number of methods for assaying alkaline phosphatase, which primarily measure the phosphate or alcohol products of its actions on a number of various substrates.<sup>1,3</sup> Alkaline phosphatase has been isolated from liver, bone, small bowel, kidney, leukocytes and placenta. Insignificant mild elevation of alkaline phosphatase may be found in patients over 50 years of age (up to 1.5 times normal), women in the third trimester of pregnancy (up to two times normal) and growing children (up to three times normal). The mechanism for an elevated alkaline phosphatase has been related to enhanced synthesis and to release from cell membranes by the detergent action of retained bile salts. When there is partial biliary obstruction, the alkaline phosphatase will be elevated but the patient may not itch and the serum bilirubin will be normal. In high-grade total biliary obstruction, jaundice and itching will also be present. The alkaline phosphatase may also be elevated in parenchymal liver diseases, particularly alcoholic liver disease and infiltrative diseases of the liver, particularly neoplasms. The hepatobiliary origin of alkaline phosphatase can be confirmed by the finding of parallel elevation of GGT. It is also possible to fractionate alkaline phosphatase to determine its tissue of origin, i.e., liver, bone or placenta, but this is not a practical or regularly used test.

Elevations of alkaline phosphatase have been observed most commonly in patients with hepatobiliary diseases, physiologic bone growth, and benign and malignant bone diseases.<sup>23</sup> Less common causes of an elevated alkaline phosphatase include infarction of several organs (myocardium, lung, spleen, kidney or bowel), ectopic production by carcinoma, ulcerative colitis, sepsis, hyperthyroidism, congestive heart failure and acute bone fracture.<sup>24</sup>

As is true for the aminotransferases, an elevation of alkaline phosphatase with elevation of other LFTs, such as aminotransferases or bilirubin, is most often due to hepatobiliary disease. However, the significance of an isolated mild elevation of alkaline phosphatase (less than 1.5 to 2 times the upper limits of normal) has undergone only limited investigation. Rubenstein, et al. found that most ambulatory patients with unexplained alkaline phosphatase elevation during multiphasic screening examination developed no overt disease during a two-year follow-up.<sup>25</sup> Mild liver disease without elevation

of other liver tests, bone disease or inherited elevation of alkaline phosphatase<sup>26</sup> are potential explanations for an unexplained alkaline phosphatase elevation. Lieberman and Phillips evaluated the clinical outcome of hospitalized patients with an isolated alkaline phosphatase elevation in a Veterans Affairs Hospital.<sup>24</sup> Over one-half of patients had normalization of their alkaline phosphatase during the follow-up period, usually within 1-3 months. Approximately one-quarter of these patients had no apparent explanation for the transient rise in alkaline phosphatase. Persistent alkaline phosphatase occurred in the remaining patients, most of whom had obvious diagnoses. It was noted that an elevation of greater than 1.5 times normal was associated with a greater likelihood of persistent alkaline phosphatase elevation.

In summary, mild elevations of alkaline phosphatase are common in physiologic situations such as age greater than 50, pregnancy and physiologic bone growth. In addition, a number of mild transient elevations of alkaline phosphatase occur for reasons that are unexplained or secondary to other coexistent disease processes. Finally, elevation of alkaline phosphatase greater than 1.5-fold or 2-fold, particularly when associated with abnormalities of other liver tests, strongly point to the presence of hepatobiliary disease.

#### **Gamma-glutamyltransferase**

Serum GGT is often used to confirm that an elevated alkaline phosphatase is secondary to hepatobiliary disease rather than to bone or other organ disease. Some but not all chemistry batteries include the GGT. However, routine screening may lead to the difficult problem of interpreting the significance of an isolated elevation of GGT.

GGT catalyzes the transfer of gamma-glutamyl groups from peptides such as glutathione to other amino acids.<sup>1,3</sup> GGT has been localized by histochemical techniques to both hepatocytes and the biliary tree, with the greatest concentration in the latter. Serum values of GGT are dependent on age and sex, with reference values being greater for men than for women and increasing in adults with age.<sup>1,3</sup> GGT is also present in membranes of the intestine and kidney, seminal vesicles, pancreas, heart and brain.

Serum GGT is elevated in association with hepatobiliary disease and generally parallels activity of alkaline phosphatase.<sup>27</sup> GGT may also be elevated in injury to other organs from conditions such as pancreatic disease, myocardial infarction, renal failure, chronic obstructive pulmonary disease and diabetes.<sup>1,3</sup>

Serum GGT is the most sensitive indicator of hepatobiliary disease; however, its poor specificity limits its usefulness. In addition, GGT is inducible by alcohol and a number of enzyme-inducing drugs.<sup>1,3,28</sup> In a study of 58 patients beginning phenytoin therapy, mean baseline GGT activity increased threefold by six months. The effect of alcohol was also obvious in this study in that baseline and six-month GGT activity was lowest in patients who drank no alcohol and greatest in patients who drank more than one pint per week.<sup>28</sup> Some investigators have advocated the use of GGT for the detection of surreptitious alcohol ingestion. In general, GGT levels were elevated 2-3 times the upper limits of normal in patients without clinically obvious liver disease but to 8-10 times normal in those with obvious liver disease.<sup>29,30</sup> The variable sensitivity and lack of specificity, however, suggests that GGT

levels alone are not helpful in detecting alcohol ingestion.<sup>1</sup>

In summary, the extreme sensitivity and poor specificity make the interpretation of an isolated GGT elevation fraught with difficulty. The use of alcohol or enzyme-inducing drugs will elevate GGT in the absence of liver disease. The primary clinical usefulness of GGT is to confirm the hepatic origin of alkaline phosphatase. Moreover, marked elevation suggests active alcoholic liver disease, biliary tract obstruction or hepatic metastasis.

#### **Serum Bilirubin**

Bilirubin is a breakdown product of heme, and approximately 75 to 80 percent of daily bilirubin production is derived from the breakdown of senescent red blood cells in the reticuloendothelial system. The heme molecule is catalyzed to iron, carbon monoxide and biliverdin, which is rapidly converted to bilirubin. The bilirubin molecule is lipid soluble and transported in blood bound to albumin. When bilirubin is presented to the liver, it is taken into the liver cell, conjugated with glucuronic acid and secreted. The secretion step appears to be the rate-limiting step in bilirubin metabolism and the one most affected by hepatic injury. Conjugated bilirubin is passed from the liver via the biliary tract into the gastrointestinal tract, where it either passed in stool or reabsorbed as urobilinogen.

Serum bilirubin is still measured by the original van den Bergh method. Most chemistry batteries include the total and direct (conjugated) fractions of bilirubin; the indirect (unconjugated) fraction of bilirubin can thus be calculated. Hyperbilirubinemia may result from overproduction of bilirubin; impaired uptake conjugation or excretion of bilirubin; or regurgitation of conjugated or unconjugated bilirubin from damaged liver cells or bile ducts.<sup>3</sup>

Unconjugated hyperbilirubinemia, defined by an elevated total bilirubin with normal direct bilirubin, may be explained by hemolytic anemia with overproduction of bilirubin from damaged erythrocytes or Gilbert's syndrome whose predominant defect is most likely impaired uptake of unconjugated bilirubin into the liver cell. A rare cause of unconjugated hyperbilirubinemia is Crigler-Najjar syndrome, which is caused by marked deficiency of glucuronyl transferase, the enzyme which catalyzes conjugation of bilirubin. Type I Crigler-Najjar syndrome is associated with absolute deficiency of glucuronyl transferase and associated with death in utero or soon after birth, while type II Crigler-Najjar syndrome may be associated with a longer life with serum levels of unconjugated bilirubin that may rise to quite high levels.

The most prevalent cause of isolated, mild unconjugated hyperbilirubinemia is Gilbert's syndrome, a benign abnormality of bilirubin metabolism that occurs in 7 to 10 percent of the population.<sup>1,3</sup> The elevation of unconjugated bilirubin is typically not greater than 3 mg/dl. All other liver tests are normal, and these patients are healthy. The second most likely cause of isolated mild, elevation of serum unconjugated bilirubin is hemolysis. An elevated reticulocyte count or lactate dehydrogenase will often provide clues to this underlying condition.

Conjugated hyperbilirubinemia in clinical practice is typically secondary to diseases of the liver or biliary tract and found in association with abnormalities of other LFTs. The sensitivity of the total serum bilirubin is increased by measuring the direct fraction, which may be elevated in milder forms of

chronic hepatobiliary disease while the serum total bilirubin remains normal. Isolated elevation of the as is fraction of serum total bilirubin occurs in rare inherited forms of conjugated hyperbilirubinemia such as Dubin-Johnson syndrome and Rotor's syndrome. These disorders are characterized by elevation of serum direct bilirubin that is typically not more than 5 mg/dl. The precise diagnosis of these congenital disorders of conjugated hyperbilirubinemia require utilization of a number of special tests.<sup>1,3</sup>

In summary, isolated mild elevation of serum bilirubin does not usually occur in patients with underlying hepatobiliary diseases, who typically have elevation of other LFTs. The most common cause of a mild isolated unconjugated hyperbilirubinemia is Gilbert's syndrome, with hemolysis seen considerably less commonly and Crigler-Najjar syndrome seen only rarely. An isolated elevation of the conjugated or direct bilirubin fraction is rare but may be explained by an inherited disorder of conjugated hyperbilirubinemia

such as Dubin-Johnson or Rotor's syndromes.

### Summary

When two or more liver enzymes are abnormal on a screening biochemical profile, the patient undergoing testing has a high likelihood of having hepatic or biliary tract disease. The finding of only one abnormal liver enzyme on a screening profile is a more difficult finding to interpret. Liver or biliary disease appears to be more likely with higher enzyme elevations (greater than 1.5 to 3 times the upper limits of normal) Mild elevation (less than 1.5 to 3 times normal) of a single liver enzyme may also be caused by underlying hepatobiliary disease; however, the majority of studies indicate that it may more likely be transient and resolve or be explained by laboratory error, statistical quirk, disease of other organ system, enzyme induction (GGT only) or unimportant liver disease such as fatty liver. Finally, an isolated mild elevation of serum bilirubin is usually caused by an inherited bilirubin disorder and has no major health consequence.

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