Evaluation of Elevated Liver Enzymes

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KEYWORDS

- Aminotransferase • Alkaline phosphatase
- Gamma glutamyl transferase • Liver enzymes
- Diagnostic algorithm

Activities of certain enzymes detectable in the serum, commonly called the liver enzymes, are one of the most frequently used panel of blood tests in a physician's practice. These enzymes include aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (AP), and γ-glutamyltransferase (GGT). Their uses are broad, ranging from screening for liver disease, to monitoring side effects of medications, and to determining responses to treatment for a given liver disease. Because of the widespread use of the tests, abnormal liver enzymes are encountered commonly.

When a liver enzyme is found to be abnormal, mild elevations (eg, <2–3 times of the upper limit of normal) without a symptom may be considered benign.[1] It is also well accepted that abnormal liver enzymes correlate with "hard end points" in liver disease, such as mortality and need for liver transplantation, as well as progression of fibrosis and development of hepatocellular carcinoma. Most recently, several observations have been reported that question the conventional definitions of normal and abnormal liver enzymes. These findings include data suggesting that normal ranges of liver enzymes may need to be redefined, and those showing that even a mild increase in liver enzymes correlates with an increased risk of future mortality.[2,3]

Regardless of how the normal range is defined, liver enzymes may remain normal in patients with well-established liver disease such as chronic hepatitis C, autoimmune hepatitis, and nonalcoholic steatohepatitis.[4,5] The converse may also be true in that abnormal liver enzymes may be seen in otherwise healthy subjects. Thus, it is important that liver enzymes should be interpreted within the clinical context of an individual patient.

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AMINOTRANSFERASES

AST and ALT catalyze the transfer of the α-amino group from alanine and aspartic acid to α-ketoglutaric acid, respectively.[6] AST is found in liver, cardiac and skeletal muscle, kidney, brain, pancreas, lung, leukocyte, and erythrocyte.[6] ALT exists mainly in liver and exists in low concentrations in other tissue.[7] Recently, an isoform of ALT2 has been cloned in a separate chromosome (chr. 16) from the classic ALT (chr. 8). There is a high homology (69% identical at the protein level) between the 2 isoenzymes. ALT2 has a wider organ distribution, including skeletal muscles and adipose tissue. To date, however, the clinical significance of ALT2 in the diagnosis of liver disease remains to be defined.[8]

Aminotransferase activities may be measured by several methods such as chromatography, spectrophotometry, fluorimetry, and colorimetry.[9] Although the assay results may differ slightly according to the method used, there is a high degree of correlation between the 2 most common methods, namely colorimetry and spectrophotometry, particularly near the normal range.[9]

Recently, there has been renewed attention about what constitutes the normal range for serum activities of aminotransferase, particularly ALT. Traditionally a level around 40 has been considered the upper limit of normal based on the mean and standard deviation calculated in apparently healthy reference subjects.[9] There is an increasing consensus that the conventional normal range may have been set too high, because the reference subjects presumed to be healthy may have included individuals with asymptomatic liver disease, such as nonalcoholic fatty liver disease and chronic hepatitis C. When more stringent criteria are applied to exclude subjects with a high probability of liver disease, the upper limit of the normal range becomes considerably lower. Prati and colleagues[10] analyzed samples of blood donors carefully selected to exclude those at risk of liver disease by using criteria such as normal body mass index (BMI), normal cholesterol, triglyceride, and glucose levels, and no potentially hepatotoxic medications. The upper limit of normal ALT in that study was determined to be 30 U/L for men and 19 U/L for women. Although these updated normal values are frequently cited, one may note that they way the upper limit of normal was set in that particular study was different from the usual convention. Whereas most laboratory normal ranges are taken from the middle 95%, ie, 2.5th to 97.5th percentiles of the population, Prati and colleagues[10] chose to take the lower 95th percentile as normal. The authors believe that the normal ranges proposed in that study are set too low.

Others have taken a different approach and have hypothesized that normal ALT defined in a cross section of a population may not equate with absence of disease. In other words, normal ALT is not necessarily healthy ALT. In a large population-based study from South Korea, serum ALT activity measured at baseline was correlated with subsequent mortality. In particular, compared with men with ALT less than 20 IU/L, those with ALT of 20 to 29 IU/L had a 2.9-fold increase in liver mortality and those with ALT of 30 to 39 IU/L had a 9.5-fold increase in mortality.[2] The authors also have evaluated ALT and AST activities as a predictor of future mortality. Using population-based data in Olmsted County, AST and ALT results in a given year were correlated with subsequent all-cause mortality. Similar to the data by Kim and colleagues,[3] there was a positive correlation between the standardized mortality ratio and the aminotransferase results. Further, the increase in mortality could be discerned with aminotransferase values less than the upper limit of normal set by the laboratory at that time.

Another aspect of serum aminotransferase activities that the clinician must be aware of is the variability between, as well as within, individual subjects. Several factors such as age, sex, and BMI influence its activities in subjects without known liver disease.[11] In