

Liver Enzymes

Four separate liver enzymes are included on most routine laboratory tests. They are- aspartate aminotransferase (AST or SGOT) and alanine aminotransferase (ALT or SGPT), which are known together as transaminases; and alkaline phosphatase (AP) and gamma-glutamyl transferase (GGT), which are known together as cholestatic liver enzymes. Elevations of these enzymes can indicate the presence of liver disease.

AST and ALT (Transaminases)

AST and ALT are jointly known as transaminases. They are associated with inflammation and/or injury to liver cells, a condition known as hepatocellular liver injury. Damage to the liver typically results in a leak of AST and ALT into the bloodstream.

Because AST is found in many other organs besides the liver, including the kidneys, the muscles, and the heart, having a high level of AST does not always (but often does) indicate that there is a liver problem. For example, even vigorous exercise may elevate AST levels in the body. On the other hand, because ALT is found primarily in the liver, high levels of ALT almost always indicate that there's a problem with the liver. (Conversely, a normal ALT level does not necessarily mean that the liver is definitely normal.)

Despite what one might expect, high levels of transaminases in the blood don't always reveal just how badly the liver is inflamed or damaged. This is an extremely important point to keep in mind. The normal ranges for AST and ALT are around 0 to 40 IU/L and 0 to 45 IU/L respectively. (IU/L stands for international units per liter and is the most commonly accepted way to measure these particular enzymes.) But someone who has an ALT level of 50 IU/L is not necessarily in better condition than someone with an ALT level of 250 IU/L! This is because these blood tests measure inflammation and damage to the liver at an isolated point in time. For instance, if the

liver is inflamed on the day that blood was drawn—let us say if a patient consumes an alcoholic drink a few hours prior to blood being drawn—the levels of the transaminases may be much higher than if the alcohol had not been consumed. Following the same reasoning, if the liver was damaged years before—by excessive alcohol use—the results of a blood test done today may be normal, but a damaged liver may still be present.

To confuse issues even further, there are many other factors besides liver injury that could affect the levels of AST and ALT. For example, males have higher transaminase levels than females. And, African-American men have higher AST levels compared with Caucasian men. Even the time of day that a blood sample is drawn may influence the level of transaminase elevation. People appear to have higher transaminase levels in the morning and afternoon than in the evening. Food intake does not appear to have a significant effect on transaminase levels. Thus, levels do not significantly differ in the fasting and non-fasting state. Finally, transaminase levels may vary from day-to-day.

The ratio of the ALT and AST may also provide useful information regarding the extent and cause of liver disease. Most liver diseases are characterized by greater ALT elevations than AST elevations. Two exceptions to this rule exist. Both cirrhosis and/or alcohol abuse are associated with higher AST levels than ALT levels, often in a ratio of approximately 2:1.

Elevations of the transaminases occur due to so many causes that they give the doctor only a vague clue of the diagnosis. Additional testing is required in order to determine more precisely what is wrong with the liver. Some possible causes of elevated transaminase levels include the following:

- Viral hepatitis
- A fatty liver

- Alcoholic liver disease
- Drug/medication-induced liver disease
 - Autoimmune hepatitis
 - Herbal toxicity
 - Genetic liver diseases
 - Liver tumors
 - Heart failure
- Strenuous exercise

GGT and AP (Cholestatic Liver Enzymes)

High levels of GGT and AP hint at a possible blockage of the bile ducts, or of possible injury to, or inflammation of, the bile ducts. This type of problem is characterized by an impairment, or failure, of bile flow, which is known as cholestasis. This type of liver injury is known as cholestatic liver injury, and this type of liver disease is known as cholestatic liver disease. Intrahepatic cholestasis refers to bile duct blockage or injury within the liver. Intrahepatic cholestasis may occur in people with primary biliary cirrhosis or liver cancer, for example. Extrahepatic cholestasis refers to bile duct blockage or injury occurring outside the liver. Extrahepatic cholestasis may occur in people with gallstones.

When a blockage or inflammation of the bile ducts occurs, the GGT and AP can overflow like a backed up sewer and seep out of the liver and into the bloodstream. These enzymes typically become markedly elevated—approximately ten times the upper limit of normal.

GGT is found predominantly in the liver. AP is mainly found in the bones and the liver but can also be found in many other organs, such as the intestines, kidneys, and placenta. Therefore, elevated levels of AP will indicate that something is wrong with the liver only if the amount of GGT is raised as well. Keep in mind that, GGT can be elevated without AP being elevated, as GGT is a sensitive marker of alcohol ingestion and certain hepatotoxic (liver toxic) drugs. It should be noted that for unclear reasons, people who smoke cigarettes appear to have higher AP and GGT than nonsmokers. Also, levels of AP and GGT are most accurate after a twelve-hour fast. You are beginning to get an inkling of the complexities that arise when evaluating abnormal LFTs!

Normal levels of AP range from 35 to 115 IU/L and normal levels of GGT range from 3 to 60 IU/L. Some causes of elevated AP and/or GGT include the following:

- Primary biliary cirrhosis
- Primary sclerosing cholangitis
- Nonalcoholic fatty liver disease (NAFLD)
- Alcoholic liver disease
- Liver tumors
- Drug-induced liver disease
- Gallstones

Clotting Factors and Hepatitis/Liver Disease

Prothrombin Time

The liver manufactures most of the clotting factors that the body uses to stop bleeding. The time it takes to produce a clot, called the prothrombin time (PT), generally runs from nine to eleven seconds. Vitamin K is an important factor in the blood clotting process. If the liver is very seriously damaged or if a vitamin K deficiency is present (as sometimes occurs in cholestatic liver diseases such as primary biliary cirrhosis), the PT will run much longer than normal, thereby increasing the risk of excessive bleeding. In some cases, injections of vitamin K can help the PT return to normal. Improvement of the PT with a vitamin K injection indicates that the liver is still functioning. When the PT does not normalize after a vitamin K injection, a condition known as a coagulopathy (a tendency to bleed excessively), severe liver damage, and/or liver failure may exist.

To adjust for variation among laboratories in calibrating the PT, the international ratio (INR) is often used. However, additional research is needed before the INR can be applied to people with liver disease.

Platelets

Platelets are blood cells that help the blood form clots. The spleen plays a role in the storage of platelets. In people with cirrhosis, the spleen works overtime to compensate for the decreased functional abilities of the damaged liver. This is associated with an enlarged spleen (Splenomegaly), and a low platelet count known as thrombocytopenia. A normal platelet count is 150 to 450×10^3 /microliter. If a patient has a value lower than 150×10^3 /microliter, thrombocytopenia is said to be present and cirrhosis should be contemplated as a diagnosis.

Bilirubin and Liver Disease/Hepatitis

Bilirubin is the yellow-colored pigment that the liver produces when it recycles worn-out red blood cells. Normal bilirubin levels are less than 1 mg/dl (milligram per deciliter). When levels become elevated, eyes and skin may turn yellow (jaundice), urine may appear a dark-tea color, and stools may look like light colored clay. Elevated bilirubin, while

not the most common abnormality in blood tests pertaining to the liver, is quite obvious on a physical exam, and it is the liver-related abnormality most familiar to the general public.

A phrase doctors often hear from their patients is, “I can’t have liver disease, I am not yellow.” People are often surprised to discover that most people with liver disease will never become yellow. In fact, many bilirubin elevations are not even related to liver disease at all. Bilirubin metabolism is very complex and consists of many steps. A problem with any one of these steps results in an abnormally high level of bilirubin. As it pertains to the liver, an elevated bilirubin level is usually associated with worsening liver disease or with bile duct blockage (cholestasis). Some possible causes of a high bilirubin level include the following:

- Primary biliary cirrhosis
- Primary sclerosing cholangitis
- Alcoholic hepatitis
- Hemolysis—red blood cell (RBC) destruction
- Drug-induced liver disease
- Choledocholithiasis (gallstones in the bile duct)
- Liver failure or general worsening of liver disease
- Tumors affecting the liver, bile ducts, or gallbladder
- Viral hepatitis
- Benign familial disorders of bilirubin metabolism, such as Gilbert’s syndrome (see below)

Bilirubin elevations are often associated with GGT and AP level elevations (discussed in my book). When elevated levels of bilirubin

and GGT and AP occur concurrently, a person is referred to as being cholestatic. However, if the bilirubin level remains normal and the GGT and AP remain elevated, the person is known as having anicteric cholestasis. Diseases marked by elevations of bilirubin, GGT, and AP are known as cholestatic liver diseases.

Gilbert's Syndrome

Gilbert's syndrome is a very common, albeit benign, inherited disorder of bilirubin breakdown (metabolism). It occurs in approximately 4-9 percent of the population. It is characterized by intermittently elevated bilirubin levels. The presence of Gilbert's syndrome is usually discovered when blood tests are routinely performed, or when they are performed for the evaluation of an unrelated problem, or for pre-employment or pre-insurance screening. Bilirubin levels usually rise to about 3 mg/dl, but rarely do they go any higher than 5 mg/dl. Levels typically increase during periods of fasting, stress, menstruation, or during the course of an unrelated illness or infection. Jaundice is the only abnormality found on physical exam. Some people complain of nonspecific symptoms such as abdominal discomfort, nausea or fatigue. However, some experts feel that these symptoms are due to anxiety. All other LFTs are normal. Imaging studies, such as a liver sonogram and liver biopsy are not indicated. However, they should be normal if performed. No long-term complications arise from this harmless syndrome, and no therapy is required.

Ammonia (NH₃) and Liver disease/Hepatitis

Ammonia is a product of amino acid breakdown. Increased levels of ammonia may be a sign of encephalopathy - an altered mental status associated with liver failure. Some doctors use ammonia levels to monitor the course of people with encephalopathy. However, since some studies have demonstrated a poor correlation between ammonia levels and degree of encephalopathy, its use for this purpose is controversial. Measurement of the ammonia level in people with liver disease is not recommended, as mild increases may occur with any liver

disease and are not diagnostic of encephalopathy. Finally, there are multiple factors which can artificially elevate ammonia levels, thereby skewing interpretability. Such factors include- cigarette smoking, certain medications such as valproic acid (a medication used to treat seizures), accidentally mixing the patient's perspiration with their blood sample during the blood draw, and laboratory delay in analyzing the blood sample.