KRESSER INSTITUTE
FOR FUNCTIONAL AND EVOLUTIONARY MEDICINE

Impaired Liver Function - Part One

Hey, everybody. In this presentation, we're going to talk about impaired liver function. This is obviously a broad category, and it includes frank liver disease but also reduced liver function, which is not a specific disease and occurs earlier on the spectrum of the progression to liver disease. This is a huge topic. It includes things such as nonalcoholic fatty liver disease, hepatitis, cirrhosis, and more. We're not going to cover each of these pathologies in detail. Consistent with the rest of the functional blood chemistry unit, the purpose here is to teach you to screen for issues, address functional problems that can contribute to those issues, and then know when to refer out.

1 in 4 Americans have a fatty liver.

Liver disease is the fourth leading cause of death in the U.S. among people between the ages of 45 and 54 years of age. Over five million Americans have chronic hepatitis B or hepatitis C. Three-quarters of people infected with hepatitis C don't know they have it because they can have no symptoms for years, and it often lies undetected for up to 20 to 30 years. It is the leading cause of cirrhosis and liver failure. Up to a quarter of Americans may have nonalcoholic fatty liver disease, including six million children, and nonalcoholic fatty liver disease is the most common cause of liver problems in the U.S. Each year about 21,000 Americans are diagnosed with primary liver cancer, which is one of the few cancers that is increasing in prevalence in the U.S., so you can see why it is important to screen for liver issues in new patients.

Markers of impaired liver function

Marker	Value
ALT	High
AST	High
GGT	High
LDH	High
Alkaline phosphatase	High

Given that our primary purpose is to screen for conditions, I'm going to teach you an approach to patients with abnormal liver function tests. The primary markers to consider are ALT, AST, GGT, LDH (or lactate dehydrogenase), and alkaline phosphatase. Consult the individual marker sheet in the blood chemistry handbook or online handbook for more information, but I'm going to briefly summarize them here.

Aminotransferases

Aminotransferases are a group of enzymes that catalyze the interconversion of amino acids and oxoacids by the transfer of amino groups. ALT is present in many organs and tissues, but the highest levels by far are in the liver, which makes it a more specific indicator of liver damage. AST is present in tissues with high metabolic activity, including liver, heart, and kidney. It's not specific to the liver, but liver dysfunction is the most common cause of elevated AST. Elevated aminotransferases typically reflect abnormalities in liver cells or the bile duct.

Aminotransferases

Marker	Lab range	Functional range
ALT	0–50 IU/L	0–26 IU/L (men) 0–20 IU/L (women)
AST	0–40 IU/L	0-25 IU/L (men) 0–23 IU/L (women)

As discussed previously, there is strong evidence that the lab ranges for ALT and AST are too high. Studies found much lower cutoffs are necessary to catch people with metabolic disease, for example, an upper limit for ALT of 26 for men and 20 for women and an upper limit for AST of 25 for men and 23 for women.

GGT is primarily found in the hepatocytes and biliary epithelium. It is also present in the spleen, heart, brain, and seminal vesicles to a lesser extent. It is the most sensitive marker of liver and gallbladder disease. However, due to its presence in many tissues, it is not specific for liver and gallbladder disease. Like alkaline phosphatase, GGT levels increase in the blood with hepatobiliary obstruction, but unlike alkaline phosphatase, GGT is not found in the bone. For this reason, GGT can be used as a means of confirming that high alkaline phosphatase levels are related to liver or gallbladder issues rather than breakdown in the bone.

GGT

Marker	Lab range	Functional range
GGT	0–60 IU/L	0–29 IU/L (men) 0–21 IU/L (women)

We also talked about this in the iron overload section, but GGT is a sensitive marker for metabolic dysfunction, and the lab range for GGT, which goes up to 60, is far too high. The optimal upper limit for GGT is 29 for men and 21 for women.

Lactate dehydrogenase, or LDH, plays a key role in glycolysis, gluconeogenesis, and anaerobic metabolism. It's found in virtually every cell, though levels are highest in the heart, liver, muscle, kidney, lung, and red blood cells. When cells are injured, the LDH-containing cytosol is spilled into the serum, so serum LDH levels are a good marker for tissue or cellular damage. When LDH is elevated, LDH isoenzymes, the follow-up test can help identify the cause of the elevation. The third band predominates in the liver and is indicative of liver damage. However, LDH is not as sensitive as aminotransferases for liver issues and has poor specificity even when isoenzymes are used.

LDH

Marker	Lab range	Functional range
LDH	119–226 IU/L	140–180 IU/L

The functional range for LDH is just based on a narrowing of the lab range and clinical observations rather than specific studies, so the typical lab range is 119 to 226, and the functional range is 140 to 180.

Alkaline phosphatase is derived predominantly from the liver and bones. You can run alkaline phosphatase isoenzymes as a follow-up test to determine whether the elevation originates from

the liver or bones, although as I just mentioned on the last slide, GGT and other markers of cholestasis can be used for this purpose as well. When bone disease is excluded, an elevation of alkaline phosphatase suggests biliary obstruction, injury to the bile duct, epithelium, or cholestasis. Alkaline phosphatase can also be elevated or depressed in many other conditions, including pregnancy, hypothyroidism, nutrient imbalance, and more. Consult the individual marker sheet for alkaline phosphatase for more detail.

Finally, there are rare cases of benign elevation of alkaline phosphatase that are genetically mediated and aren't related to any particular pathology.

Alkaline phosphatase

Marker	Lab range	Functional range
Alk phos	39–117 IU/L	42–107 IU/L

Alkaline phosphatase is another case of a marker where the functional range has been determined by slightly narrowing the lab range, not on specific studies, as with ALT, AST, GGT, and many other markers we've discussed previously. The lab range for alkaline phosphatase is 39 to 117, and the functional range is 42 to 107.

Before we talk about how to elevate these markers in patients without known liver disease, we need to briefly review common liver diseases and their association with specific liver enzymes. Taking a thorough history and understanding the risk factors for these various liver diseases are an important part of the differential diagnosis process.

Chronic viral hepatitis

Form	Prevalence	Risk factors	Comments
Hepatitis C	1.8% of general population; rate much higher in people with known risk factors and ALT >40 IU/L	Blood transfusions (esp. before 1992), IV drug use, cocaine use, hemodialysis, organ transplantation, birth in endemic region	Many patients will have no symptoms or mild symptoms and only mildly elevated ALT/AST; if risk factors present, early testing warranted
Hepatitis B	0.2–0.9% of general population; as high as 20% after travel to endemic areas	Same as above; more commonly transmitted sexually than Hep C	Many patients will have no symptoms or mild symptoms and only mildly elevated ALT/AST; if risk factors present, early testing warranted

Hepatitis C has the prevalence of about 1.8 percent in the general population, but the rate is much higher in people with known risk factors and with an ALT above 40. Risk factors include blood transfusions, especially before 1992; IV drug use; cocaine use; hemodialysis; organ transplantation; and birth in an endemic region. Many patients will have no symptoms or mild symptoms and only mildly elevated ALT and AST, so if risk factors are present, early testing is a good idea.

Hepatitis B occurs in somewhere between 0.2 and 0.9 percent of the general population but in as high as 20 percent of the population who has traveled to endemic areas or lives in endemic areas. The risk factors are the same for hepatitis C, but hepatitis B is more commonly transmitted sexually than hepatitis C. Many patients with hepatitis B will also have no symptoms or mild symptoms, and if risk factors are present, you want to test early for that as well.

Iron overload

Prevalence	Risk factors	Comments
Major HFE mutations: 0.25–0.5% in people of northern European descent; many lesser known mutations can also cause iron overload and elevation of liver enzymes	Northern European ancestry, genetic mutations causing excess iron storage, iron supplements	Symptoms are non-specific and may not be obvious until organ damage has occurred

The next potential cause of elevated liver enzymes is iron overload. We talked about this in detail in a separate presentation, but I'm just going to review briefly in this context here. The major HFE mutations are between 0.25 and 0.5 percent in terms of incidence in people of northern European descent, but as we discussed, there are many lesser-known mutations that can also lead to iron overload that we can't easily test for. Risk factors would be northern European ancestry, other genetic polymorphisms causing excess iron storage, and then taking iron supplements. As you know, the symptoms of iron overload are nonspecific and often missed in conventional workup, and they are not obvious until organ damage has occurred.

Alcoholic liver disease

Prevalence	Risk factors	Comments
Not known	10+ years of >5 drinks (12-oz beer, 1.5-oz spirits, 5-oz glass of wine)	Cirrhosis affects between 20–30% of heavy drinkers; early detection reduces morbidity and mortality

Alcohol is another cause of liver disease, and alcohol-related liver disease can range from fatty liver to alcoholic hepatitis with or without cirrhosis. Along with nonalcoholic fatty liver disease, alcoholic fatty liver disease is the most common cause of elevated aminotransferases. As I'm sure you remember from medical school, in alcoholic liver disease, the ratio of AST to ALT will often be 2:1

or higher. Alcoholic liver disease doesn't tend to occur unless drinking has been quite heavy. In the literature, it shows something like 10-plus years of over five drinks a day, although this is probably using the higher cutoffs for ALT and AST. I've definitely seen mild elevations in AST and ALT in patients who are consuming less alcohol than that, and I've seen correction of those enzymes when those patients are able to stop drinking. Cirrhosis affects between 20 and 30 percent of heavy drinkers, and the earlier it is detected, the better the outcome will be, as is often the case.

Nonalcoholic fatty liver disease

Prevalence	Risk factors	Comments
25% in general U.S. population; much higher in patients with type 2 diabetes and morbid obesity	Components of metabolic syndrome: abdominal obesity, insulin resistance, hyperlipidemia, hypertension, certain medications (corticosteroids, tetracycline, valproic acid, amiodarone)	Simple steatosis has a benign course, whereas nonalcoholic steatohepatitis can progress to cirrhosis in 10% to 20% of patients.

Nonalcoholic fatty liver disease actually refers to a spectrum of diseases that ranges from simple steatosis, fatty liver without inflammation, to nonalcoholic steatohepatitis, which is fatty liver with inflammation of liver cells, to frank cirrhosis. The prevalence is up to 25 percent now in the general U.S. population, which is just crazy, and it's much higher in patients with type 2 diabetes and morbid obesity. Risk factors basically include components of the metabolic syndrome, although you should be aware that it is not necessary for the patient to be overweight to have nonalcoholic fatty liver disease. In skinny-fat patients, or patients who are still lean but have increased body fat or insulin resistance, you can see nonalcoholic fatty liver in those patients. Simple steatosis has a pretty benign course, whereas nonalcoholic steatohepatitis can progress to cirrhosis in 10 to 20 percent of patients, a much more significant condition.