

# Asymptomatic Elevations of Liver Enzymes: General Workup, Fatty Liver, Other Causes

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**Asymptomatic elevations in liver function** are a very common problem in clinical practice. While dogmatic, the first rule is there is no such thing as a trivial elevation in the liver function tests. All such elevations require a working diagnosis and clinical follow-up.<sup>1</sup>

## HOW SHOULD ELEVATED TRANSAMINASES BE WORKED UP?

Elevated **liver function tests (LFT's)** can be sorted into disorders of cholestasis and disorders of hepatocellular injury. Cholestatic LFT's are characterized by an elevation predominantly in the alkaline phosphatase, while hepatocellular injury's hallmark is elevations in the AST and ALT. The practitioner, as with all clinical problems, must begin with a careful history, focusing on a detailed medication history, family history of liver disease (if any), alcohol intake, and risk factors for chronic viral hepatitis. The physical exam should focus on locating signs of chronic liver disease such as hepatomegaly, splenomegaly, ascites, edema, or spider angiomas. Finally, a directed laboratory evaluation should be undertaken including initial imaging of the liver and biliary tract when warranted.<sup>2</sup>

The person with clear signs of chronic liver disease should be referred immediately for subspecialty evaluation. Evidence for cholestasis should focus on medication toxicity, alcohol exposure, biliary tract disease, or the presence of primary biliary cirrhosis. The directed lab evaluation should include an antimitochondrial antibody and a right upper quadrant ultrasound. Evidence for hepatocellular injury should direct interest for medication toxicity, alcohol toxicity, hereditary hemochromatosis, fatty liver and/or **non-alcoholic steatohepatitis (NASH)**, or chronic **hepatitis B virus (HBV)** and **hepatitis C virus (HCV)** infection. Laboratory evaluation in this instance should include Fe/TIBC, HBsAg, HCV-Ab, and a right upper quadrant ultrasound. Ultrasound is favored as the initial screening tool vs. CT or MRI given

its widespread availability, cost advantage and safety.

To lend perspective, the most common causes of asymptotically elevated LFT's are medication or alcohol toxicity and fatty liver disease or NASH. If identified and corrected, medication or alcohol related elevations may not need referral and its associated costs, assuming the LFT's normalize with removal of the offending agent.

The diagnosis of alcoholic liver disease can be difficult given that most patients, at least initially, are reluctant to reveal an alcohol problem. The diagnosis should be suspected if the AST/ALT ratio is 2:1 or greater. In a classic study, an AST/ALT ratio greater than 2 had a 90 percent correlation with alcoholic liver disease.<sup>3</sup> This disorder is correctable assuming rehabilitation of alcohol abuse is accomplished, and the patient remains abstinent from further alcohol exposure.

Medications can cause minor and at times profound elevations in LFT's. While almost any medication has been reported to elevate liver function, common causes include statins, non-steroidal anti-inflammatory drugs, antiepileptic drugs, antibiotics, anabolic steroids and acetaminophen. Illicit drug use and herbal remedies should also be considered as causes of toxic hepatitis. Withdrawal of the offending agent will lead to resolution of toxicity, although it sometimes may take weeks and even months for complete recovery.<sup>4</sup>

## WHAT IS THE RECOMMENDED FOLLOW UP AND TREATMENT OF "FATTY LIVER" (NON-ALCOHOLIC STEATOHEPATITIS/NASH)?

The differentiation between fatty liver and NASH will need subspecialty evaluation and follow-up particularly given that NASH is a growing cause of chronic liver disease and is so common in the patient with metabolic syndrome.<sup>5</sup> The LFT's in fatty liver and NASH tend to be less than fourfold elevated. In contrast to alcohol injury, the AST/ALT ratio is less

than one. NASH is more commonly seen in women, type 2 diabetes, and obesity. At the very least, exercise and weight reduction strategies—the only proven therapy at present—can be undertaken pending subspecialty evaluation. Non-invasive imaging such as ultrasound will show fatty infiltration approximately 65% of the time if present. (CT and MRI are more sensitive but more costly.) The diagnosis of NASH can only be made via liver biopsy. Only with histology can the distinction between fatty liver—fat-laden hepatocytes—and NASH—the presence of an inflammatory portal infiltrate (and risk for secondary fibrosis)—be made. Given limited medical therapies, liver biopsy is usually reserved for cases when the diagnosis is in doubt; for example, elevated iron studies in the setting of fatty liver.

Many trials are currently underway to develop medical therapy for NASH. There is growing data for Vitamin E supplementation as an effective adjunct in the care of these patients. The primary care physician plays a crucial role in these patients by tightly controlling diabetes and any lipid abnormalities if present. Unless there is advanced cirrhosis, there should be no problem with medications that are metabolized in the liver. In the case of statins, with their own inherent ability to elevate liver function as a known and common side effect, the primary care physician should not hesitate to treat lipid disturbances aggressively. These patients require periodic regular LFT's to look for elevations above their baseline-elevated levels, as a sign of possible statin toxicity. For example, a patient with baseline LFT's of ALT=110 and AST=100 who develops an elevations in the 300 range on a statin can be presumed to be showing signs of statin related drug toxicity.

## WHICH OTHER DISORDERS OF LIVER FUNCTION MUST BE IDENTIFIED IN THE PRIMARY CARE SETTING?

Hereditary hemochromatosis is the most common adult inherited disorder but if found early, can be treated ef-

fectively, thus preventing advanced liver disease and its complications. Screening should begin with a calculation of the iron saturation—serum iron/TIBC. A saturation greater than 45% warrants checking the serum ferritin. If iron overload is confirmed, subspecialty referral is warranted. Genetic testing and a liver biopsy can be pursued. Genetic testing has not replaced liver biopsy, given that some patients who are homozygous for the HFE mutation (c282Y) do not have hemochromatosis; similarly, others may have hereditary hemochromatosis with no HFE mutations. Therapeutic phlebotomy is the treatment of choice and is well tolerated in most patients.

Finally, chronic HBV and HCV infections are very common in the United States affecting over one million and four million patients respectively. Both disorders currently have effective therapies—suppression for HBV and viral eradication for HCV. For HBV infection, viral suppressive therapies such as tenofovir and entecavir are very effective inhibitors of HBV viral replication, and prevent progression of liver damage in many instances.

For HCV infection, the next several years will see the doubling of HCV cure rates, with the potential prevention of end stage liver disease. The major challenge in

the case of HCV will be the identification of infected patients, given that only twenty five percent of the four million affected Americans have been identified. If this epidemic is to be controlled, the primary care physician will play the key role in identification of infected individuals for referral for antiviral therapy. If suspected, given a history of risk factors such as prior blood transfusion or parenteral drug use, the PCP can screen for HCV by ordering an HCV antibody test; if positive, infection can be confirmed by ordering a HCV viral RNA level with subsequent subspecialty referral.

In summary, all elevations of liver function need careful study and development of an appropriate differential diagnosis. The approach outlined will be effective in framing the work up of the most common causes of these elevations, correcting some, and diagnosing others that will require subspecialty input. If this approach does not lead to one of the more common diagnoses, subspecialty referral is warranted to exclude more unusual disorders of the liver, for example, autoimmune hepatitis, Wilson's Disease, and alpha-1 anti-trypsin deficiency, among others. Careful collaboration between the primary care physician and the subspecialist will ultimately lead to cost effective, positive patient outcomes.

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