

Approach to the patient with abnormal liver biochemical and function tests

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Although the term "*liver function tests*" is used commonly, it is imprecise and potentially misleading since many of the tests reflecting the health of the liver are not direct measures of its function.

Furthermore, the commonly used liver biochemical tests *may be abnormal even in* patients with *a healthy liver*.

Tests of Liver Function and Injury Tests based on substances released from damaged tissue

Endogenous substances released by <i>damaged hepatocytes</i>	ALT , AST , LDH
Endogenous substances reflecting <i>impaired bile flow</i>	GGT , AP , Urobilinogen
Tests based on substances <i>synthesized</i> by the liver	Albumin , Coagulation factors TGs , Cholesterolterol
Tests based on substances <i>metabolized and transported</i> by the liver	Endogenous substances (serum bilirubin, serum bile acids)

ALT is present in highest concentrations in the *liver*, and to a lesser extent within *skeletal muscle cells*.

ALT levels correlate with the degree of *abdominal adiposity*, and at least two large studies have suggested that the cutoff values should be adjusted for gender and BMI (but not age).

In children, median ALT levels range from 17 - 21 units/L in boys and 14 to 20 units/L in girls.

In adults, normal ALT levels range from 29 - 33 units/L for males(29) and 19 - 25 units/L for females(22).

In our clinical practice, we routinely initiate additional screening for liver disease if ALT elevations are persistently >40 U/L – roughly 1.5–2 times the upper limit of normal suggested by the NHANES analysis – on at least two measurements one month apart.

AST is present in the liver and other organs including cardiac muscle, skeletal muscle, kidney, and brain. In children, levels decline with age, more so in girls than boys after age 11.

Lactate Dehydrogenase: The differential diagnosis of elevated serum LDH levels includes skeletal or cardiac muscle injury, hemolysis, stroke, renal infarction, as well as acute and chronic liver disease.

Uncommon clinical situations in which serum LDH levels may be diagnostically useful include the massive and transient elevation characteristic of *ischemic hepatitis*.

Gamma-glutamyl transpeptidase is found in hepatocytes and biliary epithelial cells, as well as in the kidney, seminal vesicles, pancreas, spleen, heart, and brain.

In normal full-term neonates, serum GGT activity is six to seven times the upper limit of the adult reference range; levels then decline and *reach low levels by five to seven months of age.*

A gradual increase occurs in girls until age 10 and in boys through adolescence.

INITIAL EVALUATION

- Symptom based
- Incidental

The initial evaluation of a patient with abnormal liver biochemical and function tests includes obtaining a history to identify potential risk factors for liver disease and performing a physical examination to look for clues to the etiology and for signs of chronic liver disease.

Subsequent testing is determined based on the information gathered from the history and physical examination as well as the pattern of test abnormalities. (Sono)

ALT >45–50 twice, at least 1 month apart

- Exclude other causes for chronic hepatitis
- Imaging to rule out anatomic abnormality and confirm steatosis (ultrasound most commonly)
- If overweight or obese,
 - evaluate for comorbid obstructive sleep apnea, insulin resistance, type 2 diabetes mellitus, hypertension, dyslipidemia, polycystic ovary syndrome
 - set weight management goals and refer to dietician or multidisciplinary program as available

A thorough **medical history** is central to the evaluation of a patient with abnormal liver tests. The history should determine if the patient has had

exposure to any potential hepatotoxins
is at risk for viral hepatitis,
has other disorders that are associated with liver disease, or
has symptoms that may be related to the liver disease or
a possible predisposing condition.

Patients should be asked about conditions that are associated with hepatobiliary disease, such as

Right-sided heart failure (congestive hepatopathy),
Diabetes mellitus,
Skin pigmentation, arthritis, hypogonadism and dilated
cardiomyopathy (hemochromatosis),
Obesity (nonalcoholic fatty liver disease),
Pregnancy (gallstones),
IBD (primary sclerosing cholangitis, gallstones),
Early onset emphysema (alpha-1 antitrypsin deficiency),
Celiac disease,
Thyroid disease.

An ***AST to ALT ratio*** of 2:1 or greater

Is occasionally elevated in patients with NASH, and it is frequently elevated (although not greater than two) in patients with ***hepatitis C*** who have developed cirrhosis.

In addition, patients with ***Wilson disease*** or cirrhosis due to ***viral hepatitis*** may have an AST that is greater than the ALT, although in patients with ***cirrhosis*** the ratio typically is not greater than two.

The magnitude of AST and ALT elevations

varies depending on the cause

- **NAFLD**: AST and ALT <4 times the ULN.
- **Acute viral hepatitis** or toxin-related hepatitis with jaundice: AST and ALT >25 times the ULN.
- **Ischemic hepatitis** (ischemic hepatopathy, shock liver, hypoxic hepatitis): AST and ALT >50 times the ULN (in addition the LDH is often markedly elevated).
- **Chronic hepatitis C** virus infection: Wide variability, typically normal to less than twice the upper limit of normal, rarely more than 10 times the ULN.
- **Chronic hepatitis B** virus infection: Levels vary; the AST and ALT may be normal in inactive carriers, whereas most patients with chronic hepatitis B have mild to moderate elevations (approximately twice the ULN); with exacerbations, levels are more than 10 times the ULN.

CHRONIC, MILD ELEVATIONS, ALT > AST
(<150 U/L OR $5 \times$ NORMAL)

Hepatic Causes

α 1-Antitrypsin deficiency

Autoimmune hepatitis

Chronic viral hepatitis (B, C, and D)

Hemochromatosis

Medications and toxins

Steatosis and steatohepatitis

Wilson disease

Nonhepatic Causes

Celiac disease

Hyperthyroidism

CHRONIC, MILD ELEVATIONS, AST > ALT (<150 U/L, $<5 \times$ NORMAL)

Hepatic Causes

Alcohol-related liver injury
Cirrhosis

Nonhepatic Causes

Hypothyroidism
Macro-AST
Myopathy
Strenuous exercise

Differential diagnosis

- Medication use
- Chronic viral hepatitis (hepatitis B, C, D)
 - Hemochromatosis
- Nonalcoholic fatty liver disease
 - Autoimmune hepatitis
 - Wilson disease
- Alpha-1 antitrypsin deficiency
 - Congestive hepatopathy
- Malignant infiltration (lymphoma, or myeloma)
 - Muscle disorders
 - Thyroid disorders
 - Celiac disease
 - Adrenal insufficiency

