A Rational Evidence-based Approach to Abnormal Liver Tests


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Liver Function Tests

"misnomer"

- Does not effectively assess actual function
- Not always specific for the liver
- Limited information regarding presence or severity of complication

Liver Chemistry Tests

Liver Chemistry tests

- Noninvasive method of screening for the presence of liver dysfunction
- Pattern of lab test abnormality allows recognition of general type of disorder
- To assess the severity and occasionally allow prediction of outcome
- To follow the course of the disease, evaluate response to treatment, and adjust treatment when necessary

Limitations

- Lack of sensitivity (may be normal in cirrhosis or HCC)
- Lack of specificity (aminotransferase levels may be elevated in musculoskeletal or cardiac disease)
- Results suggest general category of liver disease, not a specific diagnosis
- Essential to use LCT as a battery of tests and repeat them over time
- Probability of liver disease is high when more than one test is abnormal or the findings are persistently abnormal on serial testing

General categories of tests

- Tests of the capacity of the liver to transport organic anions and metabolize drugs
  - Measures ability of the liver to clear endogenous or exogenous substances from the circulation
  - E.g. S bilirubin, serum bile acids
- Tests to detect injury to hepatocytes
  - All the enzyme tests
  - Most commonly done and most useful are aminotransferases and alkaline phosphatase

Schiff's diseases of the liver, 2007

General categories of tests

- Tests of the biosynthetic capacity of the liver

  Eg. S albumin, prothrombin time

- Tests to detect fibrosis in the liver

  Eg. Type 4 collagen, Fibrotest etc

- Tests for chronic inflammation or altered immunoregulation

  Eg. Immunoglobulins and specific antibodies

Schiff's diseases of the liver, 2007

Common serum liver chemistry tests

Liver chemistry test	Clinical implication of abnormality
Alanine aminotransferase	Hepatocellular damage
Aspartate aminotransferase	Hepatocellular damage
Bilirubin	Cholestasis, impaired conjugation, or biliary obstruction
Alkaline phosphatase	Cholestasis, infiltrative disease, or biliary obstruction
Prothrombin time	Synthetic function
Albumin	Synthetic function
γ-glutamyltransferase	Cholestasis or biliary obstruction
Bile acids	Cholestasis or biliary obstruction
5′-Nucleotidase	Cholestasis or biliary obstruction
Lactate dehydrogenase	Hepatocellular damage, not specific for hepatic disease

Normal values

- Alanine transaminase: 0–45 IU/l.
- Aspartate transaminase: 0–35 IU/l.
- Alkaline phosphatase: 30–120 IU/l.
- Gammaglutamyl transferase: 0–30 IU/l.
- Bilirubin: 2–17 μmol/l.
- Prothrombin time: 10.9–12.5 sec.
- Albumin: 40–60 g/l.

What is "Normal"?

Updated Definitions of Healthy Ranges for Serum Alanine Aminotransferase Levels *(Annals of Internal Medicine, 2002)*

Daniele Prati, MD; Emanuela Taioli, MD, PhD; Alberto Zanella, MD; Emanuela Della Torre, DSc; Sonia Butelli, DSc; Emanuela Del Vecchio, DSc; Luciana Vianello, MD; Francesco Zanuso, MD; Fulvio Mozzi, DSc; Silvano Milani, PhD; Dario Conte, MD; Massimo Colombo, MD; and Girolamo Sirchia, MD, FRCPath (Edin)

Context

Current upper limits (500 nkat/L [30 U/L] for women, 667 nkat/L [40 U/L] for men) for serum alanine aminotransferase (ALT) level were defined in populations that included persons with nonalcoholic fatty liver disease (NAFLD) and persons with hepatitis C virus (HCV) infection.

→ **30 U/L – women**
40 U/L – men

Contribution

This study redefined ALT limits in blood donors at low risk for NAFLD and without hepatitis B or C (317 nkat/L [19 U/L] in women, 500 nkat/L [30 U/L] in men). When applied to 209 anti-HCV–positive donors, the new thresholds had 76.3% sensitivity and 88.5% specificity in identifying patients with hepatitis C viremia compared with 55% and 97.4% for old thresholds.

→ **19 U/L – women**
30 U/L - men

Implications

Laboratories should consider revising the upper limits of normal for ALT to improve the sensitivity of this test in identifying subclinical liver disease.

- Studies on Liver chemistry tests
  - Review by Green and Flamm, 6000 papers published since 1990
  - Predominantly retrospective
  - Probabilities of test results given the disease state whereas the clinician typically starts with the LCT result and needs to know the predictive probability of the disease

How to Rationally approach Abnormal Liver enzymes?

Birmingham and Lambeth Liver Evaluation Testing Strategies (BALLETS): a prospective cohort study

RJ Ilford,[1*] L Bentham,[1] A Girling,[1] I Litchfield,[1] R Lancashire,[1] D Armstrong,[2] R Jones,[2] T Marteau,[3] J Neuberger,[1] P Gill,[1] R Cramb,[4] S Olliff,[4] D Arnold,[5] K Khan,[4] MJ Armstrong,[6] DD Houlihan,[6] PN Newsome,[6] PJ Chilton,[1] K Moons[7] and D Altman[8]

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Objective: To evaluate mildly abnormal LFT results in general practice among patients who do not have known liver disease.

Design: Prospective cohort study of 1290 patients (2 years follow-up)

Setting: Eleven primary care practices: 8 in Birmingham and 3 in Lambeth

Participants: Adults with abN LFT results who did not have pre-existing or obvious liver diseases. Eight analytes (ALT, AST, ALP, GGT, Total Protein, Albumin, Globulin, Bilirubin) were determined.

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Outcome Measures:

Interaction between clinical features, initial pattern of LFT results and,

1) Specific viral, genetic and autoimmune diseases such as viral hepatitis, hemochromatosis and PBC
2) A range of other serious diseases, such as metastatic cancer and hypothyroidism
3) “fatty liver” not associated with the above
4) Absence of detectable disease

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Results:

- Fewer than 5% of people with abN LFT results had specific disease of the liver and many of those were unlikely to need treatment.
- ALT and ALK - detect majority of serious or potentially serious diseases
- GGT – most frequently abN analyte with very high false-positive rate
- Protein levels – least frequently abN and not strongly related to any liver disease
- Viral hepatitis - 1% of patients with ALT being the most commonly abN
- 4/10 patients had fatty liver un UTZ and ALT and obesity – strongest predictors

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CONCLUSION:

- Unusual for an abN LFT result to signify a serious treatable disease.
- LFTs are often carried out for social and psychological, rather than clinical, reasons.
- AST and GGT should be reserve for patients in whom alcohol abuse is suspected.
- Country of origin is the strongest predictor of viral hepatitis,
- AbN ALT is strongly predictive of a “fatty liver”, as is obesity.
- No good evidence that single abN LFTs or ultrasound findings promote healthy behaviour.

When to refer for a specialist opinion?

- Unexplained liver abnormalities > 1.5 times normal on 2 occasions, a minimum of 6 months apart
- Unexplained liver disease with evidence of liver dysfunction (hypoalbuminemia, hyperbilirubinemia, prolonged PT or INR)
- Known liver disease where treatment beyond withdrawal of the implicating agent is required

Limdi et al. Postgrad Med J 2003;79:307-312

What tests to do before referral?

Consider the following;

- Screen for viral hepatitis
  - IgM anti HAV
  - HBsAg
  - Anti HCV
- Antinuclear antibodies
- Ceruloplasmin in pts < 40 yrs
- Iron studies - S ferritin, transferrin saturation
- US of the hepatobiliary system

Limdi et al. Postgrad Med J 2003;79:307-312

Take HOME Messages

- Initial evaluation: assess in clinical context
- Classified in 3 groups:
  - Synthetic function: albumin, clotting time
  - Cholestasis: bilirubin, ALP, GGT
  - Hepatocyte injury: ALT, AST

KEY POINTS

- Abnormal liver tests may present in an asymptomatic patient.
- A good clinical and physical examination are often rewarding.
- Liver tests often become abnormal in non-hepatic diseases.
- If a systemic approach is adopted the cause is often apparent.
- A specialist opinion should be sought when appropriate.

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