Assessment of some biochemical tests in liver diseases

By

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Significant liver damage may occur in patients who have normal findings on liver function tests.

Biochemical screening of healthy, asymptomatic people has revealed that up to 6% have abnormal liver enzyme levels.
Liver Function Test

- Interpretation must be performed within the context of the patient’s risk factors, symptoms, concomitant conditions, medications, and physical findings.

- Rarely provide specific Dx, but rather suggest a general category of liver disease.

- Differing laboratories → differing normal values.
LFT’s

- Markers of hepatocellular damage
- Cholestasis
- Liver synthetic function
Liver Function Test

**Advantages**
- sensitive, noninvasive method of screening liver dysfunction
- pattern of laboratory test abnormalities to recognize type of liver disorder
- assess severity of liver dysfunction
- follow cause of liver disease

**Disadvantages**
- lack sensitivity
  - normal results in serious liver disease
- not specific for liver dysfunction
- seldom lead to specific diagnosis
<table>
<thead>
<tr>
<th>Liver chemistry test</th>
<th>Clinical implication of abnormality</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT</td>
<td>Hepatocellular damage</td>
</tr>
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</tr>
<tr>
<td>Bilirubin</td>
<td>Cholestasis, impair conjugation, or biliary obstruction</td>
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<td>ALP</td>
<td>Cholestasis, infiltrative disease, or biliary obstruction</td>
</tr>
<tr>
<td>PT</td>
<td>Synthetic function</td>
</tr>
<tr>
<td>Albumin</td>
<td>Synthetic function</td>
</tr>
<tr>
<td>GGT</td>
<td>Cholestasis or biliary obstruction</td>
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</table>
Serum enzyme tests

They indicate type of liver injury: Hepatocellular or cholestatic

They direct the choice of the serological and imaging tests
SGPT & SGOT
Markers of Hepatocellular damage (Transaminases)

- **AST** - liver, heart skeletal muscle, kidneys, brain, RBCs
  - Clearance performed by sinusoidal cells, half-life 17hrs

- **ALT** – more specific to liver, very low concentrations in kidney and skeletal muscles.
  - Half-life 47hrs
Causes of abnormality of SGPT & SGOT

- Viral hepatitis.
- Nonalcoholic steatohepatitis.
- Autoimmune hepatitis.
- Alcohol related liver injury.
- Drug induced hepatitis.
SGPT & SGOT

- **Minor increase (< 2 times)**
  - Obesity
  - Fatty liver
  - Drugs

- **Mild increase (2 to< 5 times)**
  - Alcohol
    - SGOT / SGPT ratio
    - SGOT rarely exceeds 300 i.u./ml
    - SGPT > 500 → not alcoholic
    - Abstinence 6-8 weeks → normal enzymes
Mild increase (2 to < 5 times)

- **Drugs**
  - Stop and retest
  - Risk benefit analysis may be needed

- **Chronic HCV & HBV**
  - SGOT / SGPT < 1
  - < 5 times

- **NASH**
  - SGOT / SGPT <1
  - Isolated increase SGPT
SGPT & SGOT

- **Moderate increase (5-15 times)**
  - Acute viral hepatitis (A & B)

- **Severe increase (>15 times)**
  - Acute viral hepatitis (A & B)
  - ICU & serious cardiac dysfunction
  - Chemotherapy
  - Fulminant liver failure (early stages)
Ischemic hepatitis

= Shock liver, acute hepatic circulatory insufficiency.

- low-flow hemodynamic state
  - hypotension, sepsis, cardiac arrhythmia, MI, HF, hemorrhage, extensive burns, severe trauma, heat stroke

- hypotension often not documented

- usually subclinical
Ischemic hepatitis

- sudden and massive (>2000) elevation of liver enzyme, tend to decrease rapidly and return normal within 1 wk.
- mild and transient elevation of bilirubin (80% < 2 mg/dl) and ALP
- Rx and prognosis α underlying disease
Ischemic hepatitis

Fig. 3: Schematic representation of the rate of change of aminotransferase and bilirubin levels in a patient with acute ischemic hepatitis (green area, yellow area respectively) and acute viral hepatitis (blue area, orange area respectively). It is important to underscore that the pattern of enzyme alteration may vary and occasionally appear similar if a single observation point is taken into consideration (arrows).
Cirrhotic patients may have normal enzymes.

Severe lipemia can cause elevation in SGPT, less elevation in SGOT, but does not affect GGT.
SGPT & SGOT

SGOT/SGPT > 1

- Alcoholic (If AST > 500 consider other cause).
- Wilson D.
- Advanced cirrhosis
- D.D.B. treatment
The aspartate aminotransferase platelet ratio (APRI) index

You divide AST by the ULN of AST, divide this result by the platelet count (with the last three zeros chopped off), and multiply by 100. As a formula it's (AST/ULN)/platelets x 100.
Here's an example of how it works, for an AST of 63 (UNL=42) and a platelet count of 137,000/dl.

\[
\frac{63}{42} = 1.5 \\
\frac{1.5}{137} = 0.109 \\
0.109 \times 100 = 1.09 \text{ (APRI)}
\]
What does an APRI score of 1.09 tell me?

APRI comes with two cut-offs: a lower one, 0.5, and a higher one, 1.5.

If the APRI score is less than or equal to 0.5, you have no fibrosis or just a little.

If your APRI score is 1.5 or above, you probably have cirrhosis.

APRI scores between 0.5 and 1.5 are related to progressive fibrosis stages, like Metavir F1-to-F3.
Alkaline phosphates (ALP)

*Sources:* Liver, bone, kidneys, small bowel & placenta

Non hepatic causes of ALP elevation

- Old age
- Females after menopause
- Third trimester of pregnancy
- After heavy fatty meal
- Benign familial elevation
GGT may be necessary to evaluate the origin of ALP
Alkaline phosphates (ALP)

Hepatic causes of ALP elevation

- **Cholesatic**
  - CBD stones
  - PBC
  - PSC
  - Drugs

- **Infiltrative**
  - Tumours
  - T.B
  - Sarcoidosis
Alkaline phosphates (ALP)

- Depressed ALP
  - Hypothyroidism
  - Pernicious anaemia
  - Zinc deficiency
Suggested algorithm for evaluating a raised s.alkaline phosphatase

Raised ALP
  ↓
GGT increased

No
  ↓
Non-hepatic causes

Yes
  ↓
ALP twice normal
  ↓
PT symptomatic
  ↓
Persistent increase >3 months
  ↓
Liver ultrasound

Bile duct dilatation
  ↓
Yes
  ↓
ERCP

No
  ↓
Antimitochondrial antibody
  ↓
Consider liver biopsy or MRCP depending on other findings on ultrasound

Liver mass
  ↓
Yes
  ↓
Further investigation
GGT

- GGT is a sensitive indicator of hepatobiliary disease
- It is not specific
- GGT elevation excludes a bone source of ALP
- Isolated increased GGT may be of no benefit.
**Gamma-GT** – hepatocytes and biliary epithelial cells, pancreas, renal tubules and intestine

**Very sensitive but Non-specific**

Raised in ANY liver disease either hepatocellular or cholestatic

Usefulness limited

Confirm hepatic source for a raised ALP

Alcohol

Isolated increase does not require any further evaluation
GGT

GGT increased in:

- Hepatic metastasis
- Renal failure
- Myocardial infarction
- Pancreatic diseases
- Diabetes mellitus
- Drugs
Bilirubin

- Product of hemoglobin breakdown

- 2 Forms
  - Unconjugated (indirect)- insoluble
    - ↑ in hemolysis, Gilbert syndrome, meds
  - Conjugated (direct)- soluble
    - ↑ in obstruction, cholestasis, cirrhosis, hepatitis, primary biliary cirrhosis, etc.
S.bilirubin

- Increased in both cholestatic and hepatocellular disease with rise of liver enzymes.
- Unconjugated bilirubin is increased with normal enzymes in Gilbert’s disease
Diagnostic approach in elevated serum bilirubin

- Elevated bilirubin
  - History and PE
    - Unconjugated bilirubin: normal ALP, ALT, AST
      - Hemolysis studies, review medications, Gilbert
    - Conjugated bilirubin
      - Normal ALP, ALT, AST
      - Rotor’s syndrome
      - Dubin-Johnson syndrome
      - AST, ALT predominate
      - As elevated ALT evaluation
        - U/S present
        - As elevated ALT evaluation
          - Review medications, AMA, ERCP, liver biopsy
      - Abnormal ALP, ALT, AST
      - AST, ALT predominate
      - ALP predominate
      - As elevated ALT evaluation
        - U/S absent
S. albumin:

- Accounts for 65% of S. proteins.
- Normal liver produces 10-12gm/day
- Cirrhotic liver produces 4 gm/day
- Albumin half life is 22 days
- Patient with fulminant hepatitis may die with normal s. albumin.
S.albumin

Factors affecting s. albumin:
- Chronic liver disease
- Renal insufficiency
- Urinary protein losses
- Gastrointestinal losses.
Modified Child-Turcotte-Pugh prognostic classification for grading degree of hepatic dysfunction in patients with cirrhosis

<table>
<thead>
<tr>
<th>Factor</th>
<th>Points*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Encephalopathy (grade)</td>
<td>0</td>
</tr>
<tr>
<td>Ascites</td>
<td>None</td>
</tr>
<tr>
<td>Bilirubin (mg/dL)</td>
<td>1-2</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>≥3.5</td>
</tr>
<tr>
<td>Prothrombin time (sec)</td>
<td>1-4</td>
</tr>
</tbody>
</table>

*Total points = 5 or 6, grade A; 7 to 9, grade B; 10 to 15, grade C.
Nonhepatic causes of abnormal liver function test results

<table>
<thead>
<tr>
<th>Test result</th>
<th>Nonhepatic causes</th>
<th>Discriminating tests</th>
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<tbody>
<tr>
<td>Decreased serum albumin level</td>
<td>Protein-losing enteropathy</td>
<td>Serum globulins, alpha_{1}-antitrypsin clearance</td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
<td></td>
<td>Urinalysis, 24-hr urinary collection for protein</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td></td>
<td>Cardiac examination, two-dimensional echocardiogram</td>
</tr>
<tr>
<td>Elevated AST level</td>
<td>Myocardial infarction</td>
<td>ECG &amp; CK.</td>
</tr>
<tr>
<td>Muscle disorders</td>
<td></td>
<td>CK, ESR</td>
</tr>
<tr>
<td>Elevated ALP level</td>
<td>Bone disease</td>
<td>GGT, serum leucine aminopeptidase, 59-nucleotidase</td>
</tr>
<tr>
<td>Pregnancy</td>
<td></td>
<td>GGT, 59-nucleotidase, hCG in serum and urine</td>
</tr>
<tr>
<td>Malignant tumor</td>
<td></td>
<td>Alkaline phosphatase electrophoresis</td>
</tr>
<tr>
<td>Elevated bilirubin level</td>
<td>Hemolysis</td>
<td>Reticulocyte count, peripheral smear, LDH, haptoglobin</td>
</tr>
<tr>
<td>Sepsis</td>
<td></td>
<td>Clinical setting, blood cultures</td>
</tr>
<tr>
<td>Ineffective erythopoiesis</td>
<td></td>
<td>Peripheral smear, urine bilirubin, hemoglobin electrophoresis, bone marrow aspiration and biopsy</td>
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</table>
FibroTest
&
ActiTest
FibroTest

Combines the blood measurement of five indirect markers of fibrosis

- Alpha 2-macroglobulin.
- Haptoglobin
- Apolipoprotein A1
- Total bilirubin
- Gamma glutamyl transpeptidase (GGT) adjusted for age and sex
ActiTest

- FibroTest (combines the same markers with)
- Alanine aminotransferrase (SGPT)
- The algorithm adjusts the results for age and sex
<table>
<thead>
<tr>
<th>Fibrosis stage (Metavir score)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>F0:</strong> No Fibrosis</td>
</tr>
<tr>
<td><strong>F1:</strong> Portal Fibrosis</td>
</tr>
<tr>
<td><strong>F2:</strong> Bridging Fibrosis with few septa</td>
</tr>
<tr>
<td><strong>F3:</strong> Bridging Fibrosis with many septa</td>
</tr>
<tr>
<td><strong>F4:</strong> Cirrhosis</td>
</tr>
</tbody>
</table>
Necroinflammatory activity grade (Metavir score)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>A0</td>
<td>No activity</td>
</tr>
<tr>
<td>A1</td>
<td>Minimal activity</td>
</tr>
<tr>
<td>A2</td>
<td>Moderate activity</td>
</tr>
<tr>
<td>A3</td>
<td>Severe activity</td>
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What are the most frequent causes of FibroTest - ActiTest false positives?

An isolated very abnormal value of one component of FibroTest - ActiTest is suspect.

- Hemolysis, which decreases haptoglobin as observed with ribavirin treatment, or cardiac prosthesis.
- Gilbert syndrome, which increase total bilirubin.
- Extra-hepatic cholestasis, which increases GGT and total bilirubin.
- Drugs which increase total bilirubin as atazanavir.
- During combined treatment (IFN) & ribavirin therapy.
What are the most frequent causes of FibroTest - ActiTest false negatives?

- An isolated very abnormal value of one component of FibroTest - ActiTest is suspect.
- Acute inflammation, which increases haptoglobin as observed with acute sepsis.
Investigation of Abnormal LFTs

PRINCIPLES

- 2.5% of population have raised LFTs
- Normal LFTs do not exclude liver disease
- Interpret LFTs in clinical context
- Take a careful history for risk factors, drugs (inc OTCs), alcohol, comorbidity, autoimmunity
- Physical examination for liver disease
- If mild abnormalities and no risk factors or suggestion of serious liver disease, repeat LFTs after an interval (with lifestyle modification)
Investigation of Abnormal LFTs - Raised ALT / AST

- In Egypt please do Hepatitis serology markers (B, C)
- Iron studies – transferrin saturation + ferritin
- Autoantibodies & immunoglobulins
- Consider caeruloplasmin
- Alpha-1- antitrypsin