Interpreting abnormal liver function tests (LFTs) and trying to diagnose any underlying liver disease is a common scenario in Primary Care.

Chronic liver disease is often asymptomatic and the first sign of liver damage may be a raised liver enzyme in an otherwise well patient. It is therefore important for clinicians to investigate appropriately in order to diagnose and treat such patients. Alternatively, there may be nothing wrong with the liver at all - traditionally 'normal' values are defined as being within ± 2 standard deviations meaning that 2.5% of a healthy population will have LFTs outside the normal range.

This is a guideline to assist GPs in deciding how to proceed when confronted with abnormal LFTs.

The adult reference ranges for liver function tests are as follows:

- **Bilirubin**: 0-17 µmol/L
- **ALT**: 5-40 IU/L
- **ALP**: 25-115 IU/L
- **Total Protein**: 60 – 85 g/L
- **Albumin**: 38 – 50 g/L
- **gGT**: 0-32 IU/L

**Individual LFTs**

**Bilirubin**

Hyperbilirubinaemia can be broadly defined due to the whether the increase is conjugated or unconjugated. Many patients have a mixed picture. Enzyme analysis will point to the correct diagnosis and appropriate referral. Slight increases in bilirubin (17-30 µmol/L) are not unusual and usually not clinically significant.

The actual determination of conjugated (Direct) and unconjugated (Indirect) bilirubin is seldom required in adults, except when the rise in bilirubin is isolated, i.e. the liver enzymes are within the reference range.

**Causes of isolated unconjugated hyperbilirubinaemia:**

- Gilbert’s syndrome (bilirubin level usually < 70 µmol/L)
- Stress/fasting
- Drugs e.g. rifampicin, sulfonamides
- Haemolytic disease

**Causes of isolated conjugated hyperbilirubinaemia:**

- Drugs e.g. phenothiazines, sulfonamides and carbimazole
- Dubin-Johnson syndrome
- Rotor’s syndrome

This is the most common cause and effects 2 – 7 % of the population
Bilirubin Raised

Other LFTs abnormal

Follow Guidelines Below

Isolated hyperbilirubinaemia

>30 µmol/L

<30 µmol/L

Check conj/unconj bilirubin, FBC, reticulocyte count, LDH, haptoglobins

No haemolysis
Mostly unconj bilirubin >70%

Likely Gilbert’s syndrome

Haemolysis
Mostly unconj bilirubin >70%

Unlikely to be clinically significant, consider repeat after 3m

Mostly conj
Bilirubin >50%

Rare (?drugs, Dubin-Johnson, Rotor syndrome)

Haemolysis
(Consider Haem referral)
**Alanine Transferase (ALT)**

ALT is a cytosolic enzyme, which is expressed predominantly in liver cells and is used as a marker to assess liver cell damage.

ALT < 120 IU/L: generally considered mild  
ALT > 120 IU/L: generally considered severe

*Please remember that some patients can have severe liver disease with only slightly abnormal liver enzymes.*

Common causes:
- Alcohol
- Viral hepatitis
- Steatosis
- Medications/toxins e.g. NSAIDs, antibiotics, statins, antiepileptics, antituberculosis drugs

Less Common causes:
- Autoimmune hepatitis
- Haemochromatosis
- Alpha_1_-antitrypsin deficiency
- Wilson’s disease

Non-hepatic causes of raised ALT (usually small rises, <120 U/L):
- Coeliac disease
- Strenuous exercise
- Muscle disease
- Endocrine disease e.g. Hypo- and hyper-thyroidism

**Aspartate Aminotransferase (AST)**

AST is expressed in the liver, as well as in the heart, skeletal muscle, kidneys, brain and red blood cells and therefore is not as liver specific as ALT. AST and ALT differ in their cellular location within the liver, as ALT is predominantly cytoplasmic and AST is present in both cytoplasm and mitochondria.

AST is not part of the initial LFT, but the ratio of AST to ALT may provide useful information about the possible cause of liver disease:

AST:ALT ratio ≥ 2.1 may be suggestive, but not diagnostic of alcohol related liver disease, while AST:ALT ratio < 2.1 may suggest hepatic steatosis or chronic viral hepatitis.
Raised ALT

History & Examination

ALT > 120 IU/L?

Symptoms or signs?

Clinical concerns?

Abnormal Bilirubin, ALP, Albumin or PT

NO – TO ALL THE ABOVE

YES – TO ANY OF THE ABOVE

Offer lifestyle advice (alcohol, weight loss) and recheck in 3 months. If still raised, further investigations:

Liver Ultrasound
AST
CK
TFT
Fasting Lipids
HbA1c
Coeliac Serology
Ferritin
Immunoglobulins
Liver Autoantibodies
Hepatitis serology (HBsAg, anti-HCV Ab)
Alpha-1-antitrypsin
Caeruloplasmin (if < 50y)

All screening tests negative, and features of the metabolic syndrome (obesity, diabetes, raised lipids)

YES

Probable fatty liver disease

Refer to Hepatology

NO

For asymptomatic patients age < 50y, ALT <120 and AST/ALT ratio < 0.8 the risk of significant fibrosis is minimal. Offer further diet, exercise and safe drinking advice and repeat LFT including AST in 3-5yrs. It is safe to prescribe a Statin where indicated for CV risk reduction. ALT rises < 2 fold from baseline do NOT require referral.
Alkaline Phosphatase (ALP)

The two main sources of ALP are liver and bone, although there are also intestinal and placental isoforms.

Elevations may be physiological or pathological.

Common causes for raised ALP:

**Physiological**
- Third trimester of pregnancy
- Adolescents, due to bone growth
- Benign, familial

**Pathological**
- Bile duct obstruction
- Primary biliary cirrhosis
- Primary sclerosing cholangitis
- Drug induced cholestasis, e.g. anabolic steroids
- Metastatic liver disease
- Bone disease e.g Pagets
- Heart failure

Gamma-Glutamyl Transferase (γGT)

γGT is a sensitive marker for hepatobiliary disease, but its use is limited by poor specificity. Causes of raised γGT:
- Hepatobiliary disease (often with other liver enzyme abnormalities)
- Pancreatic disease
- Alcoholism
- Chronic obstructive pulmonary disease
- Renal failure
- Diabetes
- Myocardial infarction
- Drugs, e.g. carbamazepine, phenytoin and barbiturates and oral contraceptive pill

The use of γGT is in supporting a hepatobiliary source for other raised liver enzymes, e.g. ALP. It has limited utility as a primary liver test. If an isolated raised γGT is found, consider retesting after 3m if mildly raised (<5 times ULN). Consider ultrasound if γGT is >5x ULN.
Liver Ultrasound
AST
TFTs
Fasting lipids, HbA1c
Coeliac serology
Ferritin
Immunoglobulins
Hepatitis serology (HBsAg, anti-HCV Ab)
Alpha-1-antitrypsin
Caeruloplasmin (if <50y)

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HEPATOLOGY REFERAL
Albumin

Albumin synthesis is an important function of the liver. When the functioning capacity of the liver decreases, falls in plasma albumin can be seen. However, there are many other causes of decreasing albumin levels.

Causes of low albumin:

- Decreased Synthesis - severe liver disease, malabsorption, malnutrition, acute phase reaction
- Haemodilution - pregnancy, iv therapy, congestive cardiac failure, cirrhosis, antidiuresis
- Altered distribution - injury, infection, inflammation, malignancy, cirrhosis
- Loss from body - skin (burns), gut (protein losing enteropathy) and renal (nephrotic syndrome)
- Increased catabolism - acute/chronic illness, malignancy, pregnancy

History and Investigations

A detailed clinical assessment is very important for patient management and should include the following:

- Alcohol Consumption
- Medications
- Past history of autoimmune conditions
- Occupational exposure to toxins
- Family history of liver disease
- Risk factors for viral hepatitis:
  - intravenous drug use
  - travel history
  - non-sterile ear or body piercing
  - tattoos
  - health care intervention in developing nations
  - country of birth

Second Line Tests (Liver screen):
- Liver Ultrasound
- AST
- γGT
- Immunoglobulins
- CK
- Ferritin
- TFTs
- Fasting Lipids
- Glucose / HbA1c
- Coeliac Serology
- Hepatitis serology (HBsAg, anti-HCV Abs)
- Liver Autoantibodies
- Alpha-1-antitrypsin
- Caeruloplasmin (if < 50y)

References


