Blood tests used to investigate liver, thyroid or kidney function and disease

In this third article in a series on clinical testing, Pamela Mason describes three types of blood test performed by chemical pathology departments.

The previous article in this series (PJ, 3 April p419–21), looked at general blood tests requested from haematology departments, such as full blood counts. Blood tests are used to investigate many aspects of health and disease. Some tests are done routinely, for example, tests for blood type and phenylketonuria in new-born babies.

Another example is when a patient has a suspected myocardial infarction. His or her levels of cardiac enzymes, such as creatine kinase (especially the MB isoenzyme) and proponin T, will be determined and this information will be used (in conjunction with electrocardiogram changes) to diagnose underlying disease and choose an appropriate treatment. Blood tests can even be used to assess a person’s risk of a heart attack (eg, tests for c-reactive protein and homocysteine).

Venous blood can be taken for microbiological tests (eg, blood cultures in cases of suspected sepsis) and immunological testing (eg, detecting rheumatoid factor when arthritis is suspected). Tests commonly requested from chemical pathology laboratories include those for renal, liver and kidney function as well as tests for cholesterol, triglycerides and glucose and drug assays.

Liver function tests

Liver function tests (LFTs) are a group of biochemical measurements that are used to identify patients who are suffering from liver or biliary tract disease. Substances measured include:

- Albumin
- Bilirubin
- Alanine aminotransferase (ALT)
- Aspartate aminotransferase (AST)
- Gamma-glutamyl transferase (GGT)
- Alkaline phosphatase (ALP)

None of the above tests is specific for liver or biliary disease and other diseases can cause abnormal levels of one or more of these substances. Even in cases of liver disease, blood levels of one or more of these substances might be within the reference range. However, it is unlikely that all the results would be within their respective reference ranges. Together, therefore, the combination of tests is more useful than a single test.

Liver enzymes (ALT, AST, etc) leak into the blood when liver cells are damaged, so, strictly speaking, these tests indicate liver disease rather than liver function. ALT and AST levels provide an indication of the degree of inflammation as well as the possible causes or hepatic cellular damage. Similarly, ALP and GGT increases can suggest the presence of obstructive liver disease.

Panel 1 shows typical adult reference ranges for LFTs (ie, values in healthy people). Ranges vary between men and women, at different times of the day and will change with age. This needs to be recognised when tests are performed over time. So, if monitoring liver function rather than diagnosing disease, it is recommended that tests are consistently (ie, always in the morning or always in the afternoon).

Patients are usually advised to fast for four to eight hours before blood samples are taken for liver function testing because eating can affect test results. For example, having a meal can stimulate intestinal ALP release.

Patients might also be advised to stop taking drugs that could affect test results. However, many such drugs should not be stopped. For example, the enzyme inducer phenytoin can increase GGT and ALP levels, but stopping it could result in loss of epileptic control. The effect of phenytoin on test results are only usually a concern if enzyme levels exceed those normally considered asymptomatic. In such cases, an alternative test should be used, if possible. For example, some laboratories suggest that the protase leucine aminopeptidase is measured instead of GGT. However, testing serum for leucine aminopeptidase is generally not as sensitive or as convenient as testing for other liver enzymes and the levels of this enzyme can also be affected by some drugs (eg, oestrogens and progesterones). Unlike other liver enzymes, leucine aminopeptidase can be measured in urine.

If you are asked for advice about LFTs, you should remember that as many as 5 per cent of healthy, asymptomatic people can have liver enzyme levels outside their reference ranges. To diagnose liver disease reliably, information in addition to LFT results, such as from physical examination, patient history, biopsy or radiologic studies, is needed.

Albumin

Albumin levels are low in chronic liver disease. Samples are centrifuged to separate blood cells from serum and the albumin in the serum is measured. Typically, dyes such as bromocresol green or purple are added to the serum. These attach to albumin molecules, changing the light absorbency of the dye in proportion to the amount of albumin present.

Albumin is made from amino acids and accounts for around 60 per cent of plasma protein. Serum albumin level indicates how well the liver is making proteins (ie, a test of...
Albumin levels also decrease in pregnancy and after exercise. Increases in bilirubin levels are particularly suggestive of disease of the bile ducts, but there are many other causes of raised bilirubin levels in adults:

- Diseases associated with damage to hepatocytes, such as acute or chronic hepatitis, cirrhosis, primary liver cancer, liver metastases (these lead to a reduced capacity to conjugate bilirubin for excretion)
- Diseases causing restriction of bile flow and, consequently, reduced bilirubin excretion (eg. cholestasis, gallstones obstructing the bile duct and carcinoma of the pancreas)
- Diseases causing increased red blood cell destruction and, therefore, increased bilirubin production (eg. haemolytic anaemias)

In healthy individuals, almost all serum bilirubin is in the unconjugated form. As levels rise above 35μmol/L, the patient becomes visibly jaundiced. In severe jaundice, bilirubin levels can rise to 500μmol/L or higher. Determination of the ratio of conjugated to unconjugated bilirubin can give some indication of the cause of the jaundice. If the proportion of conjugated bilirubin is high, this suggests biliary obstruction. If the proportions are about equal, hepatocellular damage is likely.

Total and conjugated bilirubin are usually measured (see Panel 1). Total bilirubin is unconjugated plus conjugated bilirubin. Conjugated (direct) bilirubin can also be measured using urine samples collected over 24 hours.

Examples of drugs that increase bilirubin measurements include allopurinol, some diuretics and theophylline. Penicillin can decrease bilirubin measurements.

**Alanine aminotransferase** The enzyme ALT is present in high concentrations in the liver. It is also found in cardiac and skeletal muscle. However, ALT is considered as a specific marker of hepatocellular damage because levels are generally only significantly raised in liver disease. ALT is present in the heart and muscles in much lower concentrations — only marginal elevations occur in acute myocardial infarction.

People with acute liver damage have particularly high ALT levels and those with chronic liver disease and obstructive jaundice have more modestly raised levels.

Low ALT (and AST) levels suggest vitamin B12 deficiency.

**Aspartate aminotransferase** AST is more widely distributed than ALT. It is present in the liver, heart, kidneys, skeletal muscle and red blood cells. AST levels are raised in shock. It is less specific for liver disease and is not included in liver function profiles by all laboratories. AST levels are also raised in pregnancy and after exercise.

**Gamma-glutamyl transferase** The enzyme gamma-glutamyl transferase (GGT) is present in high concentrations in the liver, kidneys, prostate and pancreas. Levels are raised in all types of liver and biliary tract disease (acute and chronic) and also in carcinoma of the pancreas. GGT level can be used to identify those with liver or biliary disease but is not useful in establishing the cause.

Measuring GGT is most useful in patients at risk of liver disease due to alcoholism. This
Panel 2: Typical adult reference ranges for thyroid function tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH</td>
<td>0.5–5.5 mIU/L</td>
</tr>
<tr>
<td>T4</td>
<td>60–135 nmol/L</td>
</tr>
<tr>
<td>Free T4</td>
<td>9.4–25 nmol/L</td>
</tr>
<tr>
<td>T3</td>
<td>1.1–2.8 nmol/L</td>
</tr>
<tr>
<td>Free T3</td>
<td>3.0–8.6 nmol/L</td>
</tr>
</tbody>
</table>

Panel 3: Typical adult reference ranges for tests for renal function

<table>
<thead>
<tr>
<th>Test</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>135–148 mmol/L</td>
</tr>
<tr>
<td>Potassium</td>
<td>3.5–5.0 mmol/L</td>
</tr>
<tr>
<td>Chloride</td>
<td>95–105 mmol/L</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>0.7–1.4 mg/dL</td>
</tr>
<tr>
<td>Creatinine clearance</td>
<td>97–137 ml/min</td>
</tr>
<tr>
<td>Blood urea nitrogen</td>
<td>7–20 mg/dl</td>
</tr>
</tbody>
</table>

is because, unlike the other liver enzymes, GGT is raised by alcohol consumption even in the absence of liver damage. Levels return to normal when drinking is stopped, but if high levels of GGT persist, it is likely that some liver damage has been sustained or that the patient is still drinking. Measurement of GGT is, therefore, useful in managing patients with alcoholic liver disease.

As well as phenytoin, phenobarbital can increase GGT levels. Clofibrate and oral contraceptives can decrease GGT levels.

Alkaline phosphatase AP is produced in the liver, bile ducts, bone and gut and widely distributed in the body. Levels of this enzyme are raised in diseases of the liver and biliary tract, with the highest levels found in obstructive jaundice.

AP is usually raised in cirrhosis and liver cancer, but levels can be within the reference range or only slightly raised in acute hepatitis. In addition, increased levels are found in some diseases of the bone (e.g., Paget’s disease, osteomalacia and bone tumours) and further tests will be requested.

Other tests for liver disease Other indicators of liver function include prothrombin time and platelet count (see PJ, 3 April 1999, 21). Proteins made by the liver are involved in blood clotting so in liver disease (especially in worsening chronic disease), prothrombin time is increased. Liver disease causes the spleen (which traps platelets) to become enlarged so that the platelet count is often reduced.

Thyroid function tests

The concentration of thyroid hormones in the blood can be measured (usually using immunoassay techniques with fluorescence or chemiluminescence as signals) and used to diagnosis and monitor thyroid disorders. The tests used vary between laboratories, but substances measured usually include:

- Total thyroxine (T4); free (biologically active) thyroxine plus protein-bound (biologically inactive) thyroxine in serum
- Total tri-iodothyronine (T3); free (biologically active) tri-iodothyronine and protein-bound tri-iodothyronine in serum
- Thyroid stimulating hormone (TSH)

Sometimes, free thyroxine (FT4) and free tri-iodothyronine (FT3) are measured separately. Typical reference ranges are shown in Panel 2. Results outside the reference ranges are found in people with hyperthyroidism and hypothyroidism. In hyperthyroidism there is:

- Increased serum T4, FT4 and T3 concentrations, although occasionally T4 and FT4 are normal and only T3 is raised
- Reduced serum TSH concentration — in severe disease TSH can be undetectable

Results expected in hypothyroidism are:

- Reduced serum T4 and FT4 concentrations (although both may be at the lower end of their reference ranges in the early stages of the disease)
- Increased serum TSH

Some medicines (in addition to antithyroid drugs or thyroxine) can affect thyroid function and, therefore, the results of thyroid function tests. This must be borne in mind when interpreting test results. Drug interactions can occur at many sites along the thyroid hormone synthesis pathway. For example:

- Dopamine and glucocorticoids decrease TSH secretion
- Lithium interferes with synthesis and decreases thyroid hormone secretion
- Amiodarone can cause hyperthyroidism because its high iodine content stimulates thyroid hormone production

In addition, some drugs can affect thyroid hormone secretion and transport. For example, oestrogens increase the concentration of serum carrier proteins and the serum concentration of T4 (androgens decrease serum T4 concentrations) and salicylates inhibit the concentration of T4 (androgens decrease serum T4 concentrations) and salicylates inhibit the concentration of T4 (androgens decrease serum T4 concentrations) and salicylates inhibit the concentration of T4 (androgens decrease serum T4 concentrations) and salicylates inhibit

Thyroid function is sometimes determined by measuring the rate at which the thyroid gland accumulates radioactive iodine.

Renal function tests

Both blood and urine tests can be used to investigate kidney function. In terms of blood samples, the substances of interest are creatinine and blood urea nitrogen (BUN).

Creatinine is a breakdown product of muscle. It is cleared by the kidneys, but only reabsorbed and secreted in small amounts.