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The Thistle QA CEU No is: **MT00025**.

Each attendee should claim **THREE** CEU points for completing this Quality Control Journal Club exercise, and retain a copy of the relevant Thistle QA Participation Certificate as proof of registration on a Thistle QA EQA.

## CHEMISTRY LEGEND

May 2009

### HEPATIC SYNTHETIC FUNCTION

Due to the complex and multiple metabolic functions of the liver, there is no single, ideal biochemical test that can fully assess the nature and severity of hepatic dysfunction. Rather, individual biochemical test can be applied to assess specific aspects of hepatic function. Thus, necrosis of hepatocytes can be assessed by measuring enzymes that have leaked into the blood through the damaged plasma membranes of the liver cells. The ability of the liver to synthesize plasma proteins produced selectively by the liver can be assessed from plasma concentrations of these proteins, keeping in mind that the concentration of each protein is influenced also by its catabolism.

Impairment of the excretory functions of the liver, including bile secretion and flow, can be indirectly assessed from increase in the plasma levels of endogenous compounds (e.g. bile salts and bilirubin) that are normally cleared by the liver and secreted in bile. The plasma levels, however, may also be affected by changes in the rates of production, intestinal absorption, enterohepatic circulation and renal excretion of these compounds. The distinctions among classes of "liver functions" tests are somewhat arbitrary, but examining the results of all these markers together often reveals patterns typical of different pathophysiological conditions, and also allows some assessment of the severity of the liver disease.

The liver has an extensive synthetic function and plays a major role in the regulation of carbohydrate, lipid and protein metabolism. Normal blood glucose concentrations are maintained during short fasts by the breakdown of hepatic glycogen and during prolonged fasts by hepatic gluconeogenesis. Protein, triglyceride, fatty acid, cholesterol and bile acid synthesis also occur in the liver.

## Protein Synthesis

The liver is the primary site for synthesis of many plasma proteins. Severe or long-standing hepatic disease will lead to decreased synthesis and decreased plasma levels of many proteins normally synthesised in the liver: albumin,  $\alpha_1$  - antitrypsin, fibrinogen, ceruloplasmin, haptoglobin, transferrin, the coagulation proteins and others. The pattern of plasma protein alterations depends on the type, severity and duration of liver injury or disease. For example, in acute hepatic dysfunction, there is usually very little change in the plasma protein profile or the total plasma protein concentration. In chronic liver disease  $\gamma$ -globulin levels increase, whereas other proteins, such as albumin, decrease. The liver responds to inflammation with increased synthesis of the acute-phase reactants (CRP,  $\alpha_1$ -trypsin, Haptoglobin, complement C3 and C4, fibrinogen and ceruloplasmin).

**Prealbumin** has an extremely short half-life ( $\approx 1.9$  days) and the concentration of prealbumin is therefore a very sensitive index of alterations in hepatic synthetic or catabolic function. Serum levels of **immunoglobulins** indirectly reflect impairment of hepatic uptake and that of the Reticuloendothelial (RE) system of the hepatic sinusoid in its function to filter incoming intestinal tract antigens from the portal venous blood. The antigens stimulate the extrahepatic reticuloendothelial system and elicit the immune response (i.e. increased antibody production). In acute viral hepatitis there is often an increase in serum  $\gamma$ -globulin concentrations. Persistence of hypergammaglobulinemia suggests the presence of chronic active liver disease.

**Ceruloplasmin** levels increase in liver diseases such as chronic active liver disease, biliary cirrhosis and haemochromatosis. Of specific interest are the decreased levels that have been noted in Wilson's disease. Serum levels of **B<sub>2</sub>-microglobulin** can be increased in hepatobiliary disease complicated by renal disease and in chronic active hepatitis and alcohol induced liver cirrhosis without renal disease. **Ligandin** is one of a class of multifunctional proteins known as glutathione transferase; its name i.e. derived from its ability to bind a wide range of ligands (small molecules). Some of the roles of ligandin are: detoxification by binding certain toxic chemicals; storage or transport of organic ions and enzymatic degradation of some compounds.

Most **coagulation proteins** are synthesized in the liver. These proteins interact in a cascade fashion to produce a fibrin clot. Two fibrinolytic proteins, plasminogen and  $\alpha_2$ -antiplasmin, and the coagulation factors II, VII, IX & X require vitamin K for post translational carboxylation within the hepatocyte. Protein C is also synthesized in the liver by a vitamin K-dependent plasma zymogen. Parenchymal liver disease of sufficient severity to impair protein synthesis and obstructive disease sufficient to impair intestinal absorption of the fat-soluble vitamin K are therefore potential causes of bleeding disorders. Because of the great functional reserve of the liver, failure of haemostasis is rarely a complication except in liver disease of long standing or of great severity. Thus the testing for a coagulation defect is not a screening procedure but rather a means of

following progress of the disease or of assessing risk of bleeding. The prothrombin time (PT) is prolonged in coagulation defects due to liver disease because it is affected by deficiencies of more than one factor.

### **Lipid and Lipoprotein Synthesis**

The liver is a major source of plasma lipoprotein production and metabolism. In acute hepatocellular injury, levels of hepatic enzymes such as lecithin-cholesterol acyl-transferase (LCAT) and hepatic triglyceride lipase (H-TGL; triacylglycerol lipase) are decreased. Patients with acute liver disease, therefore have increased levels of plasma triglycerides, a decreased percentage of cholesterol esters, and abnormal lipoprotein electrophoretic patterns. In acute viral or alcoholic hepatitis, there is an absence of  $\alpha$ - and pre-B-bands and a presence of a wide, densely staining B-band. The hypertriglyceridemia characteristic of acute hepatocellular injury is mild; there is however, accumulation of a triglyceride-rich low-density lipoprotein (LDL), which migrates in the B-region and gives rise to the broad B-bands that appear on electrophoresis. Lipoprotein abnormalities are common in chronic intra- or extrahepatic cholestasis. There are marked elevations in the plasma levels of cholesterol and phospholipids. In addition, in patients with obstructive jaundice, an abnormal lipoprotein (Lp-X) is present.

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### **References**

1. Fundamentals of Clinical Chemistry 3<sup>rd</sup> edition, NW Tietz
2. Textbook of hepatology, volume 2, J Rodes

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### **Questions**

1. Discuss how hepatic function is assessed.
  2. Discuss protein synthesis in the liver.
  3. Discuss lipid and lipoprotein synthesis.
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