Liver Function Tests



Functions of the liver

Carbohydrate and Lipid metabolism

- Gluconeogenesis / Glycogenolysis / Glycogenesis
- Cholesterol and triglyceride production

Synthetic function

- Amino acids processing and formation
- Protein synthesis
 - albumin,
 - coagulation factors (fibrinogen, prothrombin, V, VII, IX, X and XI),
 - anticoagulants (protein C, protein S, antithrombin)
 - acute phase proteins
- Bile acids (fat digestion)
- Heparin (anti-coagulant)
- Hormone production
 - somatomedins (promote growth in bone, soft tissues)
 - angiotensinogen
 - ILF-1
 - thrombopoietin

Functions of the liver

Storage Capacity

- Glycogen, vitamins A, B₁₂, D, E, K, iron, copper
- Metabolism of waste products / toxins
 - Deamination of amino acids / Ammonia processing
 - Phase 1 / Phase 2 reactions

Immune function

- Reticulo endothelial function
 - ► Kupffer cells
- IgA into digestive tract

Anatomy



Internal Anatomy of Liver







Liver problems on the wards

Sepsis

Drug overdose / poisoning

Trauma

- Accidental / Post liver resection
- Alcoholism
- Jaundice
 - Hepatitis
 - Cholecystitis

Variceal bleeding 2 portal hypertension
 Spontaneous bacterial peritonitis



Liver function tests

Confusing

- Lots of them
- Dynamic can change rapidly
- Not specific
- When high might be normal
- When low might be bad
- When normal liver might be sick
- Involves metabolic pathways I can't remember

Tests

LFTs – enzymes AST ALT GGT ALP Synthetic function Total protein / Albumin / prothrombin time Metabolism Bilirubin / glucose levels Markers of liver disease Sodium, urea, glucose, lactate, ammonia

What to do?

- History
 Examination
 Investigation
- Patterns indicative of disease process



M C Escher (Dutch graphic artist : 1898 – 1972), Known for mathematically inspired prints with impossible constructions, explorations of infinity, architecture, and tessellations.

Aminotransferases

involved with amino acid metabolism

allow transamination,

 converts an amino acid into its oxoacid by transfer of an amino (-NH2)
 require pyridoxal phosphate as a <u>coenzyme</u>.



Aminotransferases

Liver

2 aminotransferases cytoplasmic and mitochondrial ALT predominantly hepatic (cytosol), (negligible in heart/muscle/kidneys) AST (mitochondria and cytosol) in liver, also in muscles (cardiac and skeletal), kidney, pancreas and erythrocytes ALT and AST are released from liver when hepatocytes are damaged or destroyed

What to do?



- History
 Examination
 Investigation
- Patterns indicative of disease process
 If doubt measure another enzyme e.g. CK / TN
 Organise imaging/test

ALT - Alanine Transaminase

Enzyme

- Converts amino acid into pyruvate
- Predominantly in liver,
 - also in skeletal muscle, kidneys and heart

Located in cytosol

- Spilled out into plasma as liver cells die
- Usually higher than AST
- Good marker of liver inflammation
- Can be normal in sick liver
- In alcoholic liver disease usually lower than AST



ALT > AST (normal)

| I | | | |
|-----------------|-----|----|----|
| ALT | 26 | 27 | 24 |
| Albumin | *46 | 43 | 43 |
| Protein | *76 | 71 | 70 |
| Globulin plasma | *30 | 28 | 27 |
| AST | 21 | 11 | 18 |

AST > ALT ETOH disease

| Bilirubin (Total) | *320 | *299 | *248 | |
|----------------------|------|------|------|--|
| Alkaline Phosphatase | 79 | 96 | 92 | |
| GGT | 277 | 285 | 293 | |
| ALT | *30 | *35 | *37 | |
| AST | *117 | *89 | *84 | |

ALT normal in sick liver

| | Urea | 3.7 | mmol/L | 3.7-7 | .7 | |
|--------|----------------------|------|----------|-------|------|--------|
| | Creatinine | 47 | umol/L_L | 50-1 | 20 | |
| | Albumin | 45 | g/L | 35-47 | 7 | |
| | Protein | 72 | g/L | 62-80 |) | |
| | Globulin plasma | 27 | g/L | 25-35 | 5 | |
| | Bilirubin | 20 | umol/L | 2-20 | | |
| | GGT | 222 | U/L H | 0-60 | | |
| | Alkaline Phosphatase | 130 | U/L H | 40-1 | 10 | |
| \leq | AST | 46 | U/L H | < 45 | i | |
| | Amylase | 48 | U/L | 25-13 | 35 | |
| | ALT | 41 | U/L | < 45 | | |
| | | | | | | |
| lae | moglobin | 156 | g/L | | 130 | -175 |
| BC | - | 4.52 | ×10E12/ | L | 4.3- | 6.0 |
| lae | ematocrit | 0.45 | | | 0.4- | 0.52 |
| 1e | an Cell Volume | 100 | fL 🛛 | Н | 80- | 99 |
| 1e | an Cell Haemoglobin | 34.6 | pg | Н | 27- | 34 |
| ۱D | N | 14.3 | | | 11.5 | 5-15.0 |
| ۷la | telets | 119 | ×10E9/ | LL | 150 | -400 |
| ₩Bi | c | 5.5 | ×10E9/L | | 4.0- | 11.0 |
| | | | | | | |

ALT and disease

Very high levels (upto x50 normal)

- Severe necrosis, severe viral or drug induced hepatitis
- Moderately high levels
 - EBV, chronic hepatitis, cholestasis, early or improving acute viral hepatitis, CCF with hepatic congestion

Slight-to-moderate elevations

- (usually with higher increases in AST levels)
- insult producing acute hepatocellular injury, eg active cirrhosis, and drug-induced or alcoholic hepatitis
- Marginal elevations
 - acute MI, (hepatic congestion or ALT from heart)



► Two isoenzymes are present In humans:

- GOT 1 cytosolic red blood cells / muscles cytoplasm / kidneys
- GOT 2 liver mitochondria and cytosol

ALT and AST

In general,

- Increases in AST and ALT are higher with viral or toxin hepatitis than with biliary obstruction
- in viral hepatitis levels may rise upto 14 days before jaundice
- Cholestasis will increase ALT and AST when associated with hepatocellular death

Typical AST/ALT Values in Disease



Aminotransferases often normal in cirrhosis.

In uncomplicated alcoholic hepatitis, AST normally less than 500 U per L

The highest peak aminotransferase values are found in patients with acute ischemic or toxic liver injury.

Rules of thumb

- 1. The higher the AST : ALT ratio, greater likelihood alcohol contributing to abnormal LFTs
 - In alcohol the ratio is normally 2:1
 - elevated AST : ALT ratio in alcoholic liver disease results from the depletion of vitB6 (pyridoxine), needed as a cofactor
- 2. In the absence of alcohol intake, increased AST : ALT ratio often found in patients with cirrhosis
- 3. ALT level > 500 IU/L unlikely to be just alcoholic liver disease
- 4. AST:ALT ratios are suggestive of certain conditions but ratio cannot be totally relied on

ALP – alkaline phosphatase

Enzyme which dephosphorylates substrates

- Eg proteins, nucleotides, in an alkaline environment
- May have role in regulating biliary secretions

Found in all tissues

- predominantly liver (bile duct 55%),
- bone (osteoblasts 45%),
- gut (5%) / kidney / placenta

Isoforms exist –

- ALP I intestinal 5%
- ALP L tissue non specific (Liver/Kidney/Bone)
- ALP P placental

Elevated ALP ? normal = 20 - 140 iu / l

differentiate source

- are other LFTs elevated including bilirubin?
 - (electrophoresis / heat exposure) bone burns, liver lasts
- Higher ALP levels may be due to:
 - Biliary obstruction / Liver disease
 - Bone disease Healing fracture / Osteoblastic bone tumors / Osteomalacia / Paget's / Rickets
 - Hyperparathyroidism
 - Leukemia / Lymphoma
 - Sarcoidosis

Obstructive picture

| eGFR | 57 | mL/min | | |
|----------------------------|------|--------|---|-----------|
| Urate | 0.33 | mmol/L | | 0.20-0.42 |
| Phosphate | 1.13 | mmol/L | | 0.70-1.50 |
| Magnesium | 0.89 | mmol/L | | 0.70-1.00 |
| Calcium | 2.26 | mmol/L | | 2.10-2.55 |
| Calcium (albumin adjusted) | 2.34 | mmol/L | | 2.10-2.55 |
| Albumin | 36 | g/L | L | 38-52 |
| Protein | 73 | g/L | | 66-84 |
| Globulin | 37 | g/L | | 22-38 |
| Bilirubin | 46 | umol/L | Н | 0-24 |
| GGT | 473 | U/L | Н | 0-60 |
| Alkaline Phosphatase | 246 | U/L | Н | 40-130 |
| AST | 39 | U/L | | 0-45 |
| ALT | 53 | U/L | Н | < 45 |
| Amylase | 80 | U/L | | 25-135 |

Gamma glutaryl transferase

 Catalyst for transport of gamma glutaryl group from glutathione found at cell membranes

- Actual role unclear BUT
 - Glutathione free radical scavenger involved in detoxification
- Found in hepatocytes and biliary epithelial cells
- Used as "ESR" of the liver
- Increase in alcoholics and obstructive biliary disease
 - unclear why elevated in alcoholics
 - possible induction of enzymes / leakage from cells / increased oxidative stress
 - may be elevated on its own in drinkers

Alcoholic hepatitis

| | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
|----------------------|----------|----------|-----------------|----------|----------|----------|----------|----------|
| | | | | | | | | |
| ••• | 09/08/11 | 12/08/11 | <u>15/08/11</u> | 29/08/11 | 22/09/11 | 19/01/12 | 25/01/12 | 01/02/12 |
| | 11:35 | | | | | | | 09:40 |
| Total Bilirubin | 115 | 152 | 126 | 52 | 82 | 620 | 541 | 345 |
| Alk. Phosphatase | 172 | 155 | 125 | 130 | 157 | 180 | 149 | 139 |
| GGT | 904 | 848 | 664 | 323 | 769 | 585 | 243 | 167 |
| ALT | 45 | 31 | 27 | 58 | 63 | 53 | 47 | 43 |
| Total Protein | 73 | 69 | 69 | 71 | 81 | 70 | 61 | 61 |
| Albumin | 41 | 40 | 41 | 43 | 48 | 37 | 32 | 32 |
| Globulin | 32 | 29 | 28 | 28 | 33 | 33 | 29 | 29 |
| Serum Amylase | | | | | | | | 56 |
| Comment | Ø | Ø | Ø | Ø | Ø | Ø | Ø | Ø |
| Conjugated Bilirubin | | | | | | > 385 | | |
| | Ø | | | Ø | | Ø | | |
| | Ø | Ø | Ø | Ø | | | | |
| AST | 158 | | | | | | | |

Obstructive picture

| eGFR | 57 | mL/min | | |
|----------------------------|------|--------|---|-----------|
| Urate | 0.33 | mmol/L | | 0.20-0.42 |
| Phosphate | 1.13 | mmol/L | | 0.70-1.50 |
| Magnesium | 0.89 | mmol/L | | 0.70-1.00 |
| Calcium | 2.26 | mmol/L | | 2.10-2.55 |
| Calcium (albumin adjusted) | 2.34 | mmol/L | | 2.10-2.55 |
| Albumin | 36 | g/L | L | 38-52 |
| Protein | 73 | g/L | | 66-84 |
| Globulin | 37 | g/L | | 22-38 |
| Bilirubin | 46 | umol/L | Н | 0-24 |
| GGT | 473 | U/L | Н | 0-60 |
| Alkaline Phosphatase | 246 | U/L | Н | 40-130 |
| AST | 39 | U/L | | 0-45 |
| ALT | 53 | U/L | Н | < 45 |
| Amylase | 80 | U/L | | 25-135 |

Jaundice







Bilirubin

- Processing involves three steps
 - 1. Absorption
 - 2. Conjugation
 - 3. Excretion

Rate limiting step is excretionOften conjugated form in liver diseases





Causes of jaundice

- Unconjugated Bilirubinaemia
 < 20% bilirubin is conjugated
 - 1) Overproduction -
 - Haemolysis / rhabdomyolysis / ineffective erythropoiesis
 - 2) Decreased hepatic conjugation -
 - Heme enters liver, converted to bilirubin, but not conjugated
 - Bilirubin builds up blood and is filtered by the kidneys into urine

Causes

- 1. Gilberts syndrome (mild drop glucuronyl transferase)
- 2. Crigler Najar syndromes
- 3. Hepatitis viral and drugs

Causes of jaundice

Conjugated Bilirubinaemia

> 50% bilirubin is conjugated

Impaired intrahepatic secretion

- Hepatocellular disease
- Sepsis
- Cholestasis of pregnancy
- Drug induced IVN / Clavulinic acid / flucloxacillin / carbamazepine OCP / erythromycin
- Infiltrative processes (amyloid / sarcoid)

Impaired extraheptic clearance
 Mechanical obstruction (stones/tumour)

Gilberts Syndrome

| Chemistry - Serum/ | /Plasma | | | | Number of dates to display 🧏 💌 |
|----------------------|-------------------|-------------------|-------------------|----------|--------------------------------|
| | Ľ, | للخ | Ľ | | |
| | 17/05/06 | 10/08/09 | 02/09/09 | 10/02/10 | |
| | 17:00 | 10:40 | <u>14:20</u> | | |
| Bilirubin | *17 | *27 | *26 | 30 | |
| GGT | 44 | 33 | 34 | 26 | |
| Alkaline Phosphatase | 90 | 67 | 62 | 68 | |
| ALT | 26 | 27 | 24 | 14 | |
| Albumin | *46 | 43 | 43 | | |
| Protein | *76 | 71 | 70 | | |
| Globulin plasma | *30 | 28 | 27 | | |
| AST | 21 | 11 | 18 | | |
| Authorised by | Analyser Protocol | Analyser Protocol | Analyser Protocol | | |
| Sodium | 141 | 136 | | | |
| Potassium | 4.7 | 3.6 | | | |
| Glucose | | 5.3 | | | |
| Urea | 4.8 | 5.8 | | | |
| Creatinine | *102 | 73 | | | |
| eGFR | | >60 | | | |
| Lab Comment | | Ø | | | |

Acute Liver failure

► Hyperacute

onset of encephalopathy <7 days of jaundice
 Acute

encephalopathy within 8 – 28 days of jaundice
 Subacute

encephalopathy within 4 – 26 weeks

O'Grady, Lancet 1993

Causes of acute liver failure

- Viral
 Drugs / Toxins
 Vascular events
 Others
 pregnancy / Wilsons / lymphoma / trauma /
 - heat stroke

Overdoses / Poisoning



Hyperacute Liver Failure - Mushrooms

| - | 25/07/08 | 25/07/08 | 25/07/08 | 25/07/08 | 26/07/08 |
|---------------------------|----------|----------|----------|----------|---------------|
| | 12:20 | 15:00 | 19:55 | 23:15 | 05:10 |
| Sodium | 140 | 142 | 139 | 140 | 140 |
| Potassium | 7.3 | 6.5 | 3.6 | 3.5 | 3.5 |
| Glucose | 5.2 | | 10.4 | 5.7 | 4.1 |
| Urea | 7.6 | 8.6 | 8.7 | 8.3 | 7.9 |
| Creatinine | 206 | 202 | 174 | 167 | 165 |
| Phosphate | | 2.20 | 1.50 | 1.83 | 1.10 |
| Calcium | | 1.70 | 1.80 | 1.90 | 2.10 |
| Calcium (albumin adjusted |)) | 1.9 | 2.0 | 2.1 | \$ 2.3 |
| Albumin | 32 | 32 | 29 | 30 | 32 |
| Protein | 52 | 54 | 49 | 50 | 54 |
| Globulin plasma | 20 | 22 | 20 | 20 | \$ 22 |
| Bilirubin | 7 | 9 | 12 | 13 | 20 |
| GGT | 62 | 53 | 54 | 53 | 55 |
| Alkaline Phosphatase | 191 | 130 | 116 | 108 | 119 |
| AST | *3123 | *2940 | | | 7133 |
| Magnesium | | 0.87 | 0.77 | 0.75 | 0.73 |
| Troponin I | | 15.01 | 27.49 | | 45.66 |
| ALT | *3470 | *2744 | | | 5236 |

Paracetamol toxicity in chronic liver

disease.

| | | _ | | _ | | |
|----------------------------|-------------------|----------|-------------------|-------------------|-------------------|-------------------|
| ••• | 16/12/05 | 16/02/06 | 17/02/06 | 22/02/06 | 22/02/06 | 23/02/06 |
| | 17:30 | 21:39 | 09:10 | 10:30 | 19:50 | 09:15 |
| Sodium | 138 | 139 | 142 | 132 | 135 | 132 |
| Potassium | 4.0 | 3.8 | 3.6 | 4.1 | 3.4 | 2.2 Ø |
| Glucose | 5.5 | *6.2 🖉 | 5.3 | | | 16.6 |
| Urea | 3.7 | *4.7 | 4.5 | 6.3 | 7.3 | 8.6 |
| Creatinine | 47 | 28 | 41 | 80 | 86 | 94 |
| Albumin | 45 | | 38 | 37 | 31 | 27 |
| Protein | 72 | | 64 | 66 | 57 | 51 |
| Globulin plasma | 27 | | 26 | 29 | 26 | 24 |
| Bilirubin | 20 | | 24 | 204 | 157 | 192 |
| GGT | 222 | | 207 | 307 | 195 | 217 |
| Alkaline Phosphatase | 130 | | 130 | 765 | 534 | 447 |
| AST | 46 | | 48 | | *9480 U/L | >4000 |
| ALT | 41 | | 39 | *7570 U/L | *4074 U/L | 3269 |
| Glucose Comment | Ø | | | | | Ø |
| Authorised by | Analyser Protocol | | Analyser Protocol | Analyser Protocol | Analyser Protocol | Analyser Protocol |
| Amylase | 48 | | | 37 | 39 | |
| Phosphate | | | 1.06 | 1.39 | | |
| Calcium | | | 2.1 | 2.2 | | |
| Calcium (albumin adjusted) | | | 2.2 | 2.2 | | |
| Magnesium | | | | 1.02 | | |
| General Comment | | | | Ø | | |
| C-Reactive Protein | | | 14 | | | |

Paracetamol toxicity



Trauma

| | 10/05/10 | 11/05/10 | 12/05/10 | 13/05/10 | 14/05/10 | 15/05/10 | 16/05/10 | 17/05/10 | 24/05/10 | 03/10/11 |
|----------------------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|
| | 14:36 | 15:30 | 05:30 | 09:40 | 09:00 | 08:20 | 08:45 | 09:10 | 10:10 | 14:15 |
| Albumin | 43 | | 32 | 34 | 35 | 35 | 36 | 35 | 43 | 44 |
| Protein | 64 | | | | | | | | | 66 |
| Globulin | 21 🖉 | | | | | | | | | 22 |
| Bilirubin | 7 | 16 | 9 | 17 | 21 | 18 | 14 | 12 | 10 | 18 |
| GGT | 11 | | | 23 | 51 | 52 | 60 | 67 | 121 | 12 |
| Alkaline Phosphatase | 64 | | 53 | 61 | 92 | 100 | 115 | 122 | 134 | 67 |
| ALT | 15 | | | 674 | 573 | 454 | 400 | 366 | 91 | 23 |
| Sodium | 142 | 140 | 137 | 138 | 136 | 133 | 137 | 137 | 140 | |
| Potassium | 4.0 | 4.0 | 4.3 | 3.3 | 3.7 | 3.5 | 3.4 | 3.3 | 4.1 | |
| Chloride | 104 | 105 | 104 | 101 | 98 | 95 | 100 | 102 | 101 | |
| Glucose | 4.9 🖉 | 7.0 🖉 | 7.3 🖉 | 6.1 🖉 | 5.4 🖉 | 5.4 🖉 | 5.9 🖉 | 10.1 🖉 | 5.2 🖉 | |
| Urea | 6.3 | 5.5 | 4.8 | | | | | | 5.3 | |
| Creatinine | 79 | 71 | 66 | 61 | 56 | 57 | 63 | 63 | 70 | |
| AST | 13 | 90 | 568 | 252 | 150 | 89 | 98 | 100 | 27 | |
| Phosphate | | | 1.28 | | | | | | | |
| Magnesium | | | 0.71 | | | | | | | |



Lactate

Type A - Hypoxic Reduced oxygen / perfusion – Liver failure / sepsis ► Type B – Nonhypoxic 1) disease states : Sepsis / Liver disease / thiamine deficiency 2) drugs – metformin / ethanol / paracetamol 3) metabolic disorders – mitochodria eg G6PD / MELAS /

<u> Mitochondrial disease - MELAS</u>

mitochondrial encephalomyopathy, lactic acidosis and stroke like episodes



Prothrombin time

does not become abnormal until more than 80% of liver synthetic capacity is lost PT a relatively insensitive marker of liver dysfunction only based on manufacture of clotting factors and dependent on vit K stores Often useful for following liver function in patients with acute liver failure

Liver failure and prothrombin time





Liver failure and INR







Albumin

Production 10-25 g/day (upto x2 increase)

- T_{1/2} 20 days
- Albumin pool approx 5g/kg
- 60% (210g)interstitial space
- 40% (140g) intravascular
- 70% oncotic pressure due to albumin
- 7% (7g) intravascular leeks out each hour

Albumin - Functions

Transports fatty acids
Binds bilirubin
Binds drugs and hormones
Scavenges free radicals
Buffers pH

Hypoalbuminaemia

Reduced production

- Liver disease : cirrhosis and acute liver failure
- Malnutrition / Malabsorption
- Chronic renal failure
- Disseminated cancer
- Acute disease states (-ve acute-phase protein)
- Increased Loss
 - Excess excretion kidneys (nephrotic syndrome)
 - Excess loss in bowel (protein losing enteropathy)
 - Burns / Necrotising fasciitis (absence of skin barrier)
 - Pancreatitis / Sepsis
- Haemodilution (pregnancy),
- Increased Intersitial deposition
 - Increased vascular permeability (sepsis)
 - Decreased lymphatic clearance)

A - I of liver problems

- A auto immune / alcohol
- B hep B / Biliary disorder / blirubin problem / blockage
- C hep c / cholestasis
- D drugs / toxins
- E ethanol
- F fatty liver
- G growths ie cancers
- H haemodynamic disorder, CCF / cardiac tamponade, hypoxia
- I Iron and others (haemo. Wilsons a1 anti trypsin)

Surgical Sieve

VITAMIN C,D,E,F

• T

M

C

D

■ E

- V : Vascular
- I : Infective /Inflammatory
 - : Trauma
- A : Auto-immune
 - : Metabolic
- I : Idiopathic / Iatrogenic
- N : Neoplastic
 - : Congenital
 - : Degenerative/Developmental
 - : Endocrine/Environmental
- F: Functional



Questions ?