Physiology and Pathophysiology of Liver

Prof. Anil Dhawan MD FRCPCH
Director, King’s Cell Therapy Unit
Director Paediatric Liver GI and Nutrition Centre
King’s College Hospital
London
Remit of the talk

- Applied anatomy
- Synthetic functions
- Detoxification functions
- Common pathophysiology states in liver disease
  - Hepatorenal syndrome
  - Hepatopulmonary syndrome
  - Ascites
  - Encephalopathy
  - Portal hypertension
Hepatic Blood Flow

Dual blood supply
  Hepatic Artery (40%)
  Portal vein (60%)
Outflow
  Three Hepatic Veins
Formation of bile

Central function of liver
The synthesis and enterohepatic circulation of bile salts

Bile salts recirculate 6-8 times per day

Conjugated bilirubin

Haemoglobin

85% Biliverdin

15%

Unconjugated bilirubin + albumin

Myoglobin Cytochromes

Unconjugated bilirubin synthesised in the Kupffer's cells of the liver and the reticuloendothelial system

90% bile salts reabsorbed in ileum as urobilinogen

10% bile salts lost in faeces as stercobilinogen
Focal biliary cirrhosis
Role of Liver in Metabolism

- HDLP
- Ketone Bodies
- Fatty Acids
- Coenzymes: NAD, NADP, FMN, FDP, HS CoA, PALP
- Amino Acids
- Uric Acid
- Urea
- Blood Glucose
- Lactate
- Bile
- Cholesterol
- Bile Acids
- Bilirubin
- Monosaccharides
- Amino Acids
- Lipids
- Indol
- Skatol
- Phenol
- Benzoic Acid
- Glycogen
- Glucuronide
- Blood Plasma Proteins: albumin, α₁, α₂, β-Globulins
- Blood Clotting factors
- Small Intestine
- Large Intestine
- RES
• aminoacidopathies

• organic acidemia

• urea cycle disorders
Figure No. 1: DRUG METABOLISM PATHWAYS

- Oxidation (Cytochrome P450's)
- Conjugation (Glucuronidation etc.)

Metabolite

- Polar Species
- Renal Elimination (Urine)

- Stable Adducts
- Non-polar Species
- Biliary Elimination (Stool)
**FAT-SOLUBLE TOXINS**

- Phase 1
  - (Cytochrome P450 Enzymes)
  - Oxidation
  - Reduction
  - Hydrolysis
  - Hydration
  - Dehalogenation

**WATER-SOLUBLE WASTE**

- Phase 2
  - (Conjugation Pathways)
  - Sulfation
  - Glucoronidation
  - Glutathione Conjugation
  - Acetylation
  - Amino Acid Conjugation
  - Methylation

**Nutrients Needed**

- **FAT-SOLUBLE TOXINS**
  - Vitamins B2, B3, B6, B12
  - Folic Acid
  - Glutathione
  - Flavonoids

- **WATER-SOLUBLE WASTE**
  - Methionine
  - Cysteine
  - Magnesium
  - Glutathione
  - Taurine
  - Vitamin B5, B12
  - Vitamin C
  - Glycine

**Eliminated via:**
- Urine
- Bile
- Stool

**Intermediate Metabolism**
THREE PHASES OF DETOXIFICATION

PHASE I
- Exotoxins
  - P450 Enzymes
  - B Vitamins
  - Minerals
  - BCAAs
  - Bioflavonoids
  - Glutathione

PHASE II
- Glutathione Transferases
- Amino Acids
  - Intermediary metabolites
    - Reactive Molecules
      - Tissue Damage
        - Antioxidant Protection
          - Vitamins A, C, E
          - CoQ10
          - Selenium
          - Copper, zinc
  - Less Reactive Metabolites
    - Bile
      - Serum
    - Feces
      - Kidney
      - Urine

PHASE III
- Toxins excreted from the body
A:

Paracetamol

Paracetamol conjugates

Glucuronide sulfates

Excretion in urine

Conjugation non-toxic

Hepatotoxicity

CYP450 metabolism

5%

95%

Glutathione

NAPQI

Hepatotoxicity

B:

Paracetamol

Paracetamol conjugates

Glucuronide sulfates

Excretion in urine

Conjugation non-toxic

Hepatotoxicity

CYP450 metabolism

X

NAPQI

Hepatotoxicity
Detoxification Functions of Liver
. Initial Event

- Infection (bact./viral)
- Bleeding
- Intoxication
- Ischemia
- other

. Toxin-concentration

- Hydrophobic substances
  - Hydrophobic bile acids
  - Bilirubin
  - plasmatic NO
  - Prostacycline
  - Indol/Phenol-Metabolits
  - Toxic fatty acids
  - Thiols
  - Digoxin/Diazepam-like subst.

- Hydrophilic substances
  - Ammonia

Toxin Hypothesis of Liver failure:
Vicious cycle of autointoxication
Pathogenesis of NAFLD
Fatty acids

Esterification

Synthesis of Fatty acids

Oxidation
Mitochondria
Peroxisomes
Microsomes

Triglycerides

Export

VLDL

HEPATOCYTE
HEPATOCYTE

Insulin

TNF-α
Rad
PC-1
Leptin
Fatty acids

Increased uptake of fatty acids

Fatty acids

Increase in cytochrome P-450 4A
Increase in cytochrome P-450 2E1

Mitochondrial ß-oxidation overload

Lipid peroxidation

Accumulation of fatty acids

Increase in glycolysis

Synthesis of fatty acids

Hyperinsulinemia

Accumulation of triglycerides

Decrease in apolipoprotein B-100

VLDDL

Adipocytes

TNF-α
Rad
PC-1
Leptin
Fatty acids

Insulin
Adipocytes 

Increase in lipolysis 

Insulin 

TNF-α 
Rad PC-1 
Leptin 
Fatty acids 

Increased uptake of fatty acids 

Fatty acids 

Mitochondrial β-oxidation 

Acyl-coenzyme A synthetase 

Expression of uncoupling protein-2 

Diacarboxylic fatty acid 

PPAR-α 

Peroxisomal β-oxidation 

Acyl-coenzyme A 

Microsomal ω-oxidation 

H₂O₂ 

H₂O₂ 

TNF-α 

PC-1 

Leptin 

Fatty acids
Pathogenesis of NAFLD

- $\frac{1}{2} \text{O}_2 + 2 \text{H}^+ \rightarrow \text{H}_2\text{O}$
- Increased β-oxidation
- TNF-α
- Damaged mtDNA
- Over-reduction of complexes I and III
- $\text{O}_2^- \rightarrow \text{H}_2\text{O}_2$
- Lipid peroxidation products
Pathogenesis of NAFLD

ROS to Steatohepatitis

ROS

Lipid peroxidation products (HNE, MDA)
Cytokines (TNF-α, TGF-β, FasL, IL-8)

- TNF-α, FasL
  - Mitochondrial permeabilization, caspase activation
  - Cell death

- TGF-β
  - Induction of trans-glutaminase
  - Mallory bodies

- TGF-β
  - Neutrophil infiltration
  - Inflammation

- TGF-β
  - Stellate cell activation (collagen synthesis)
  - Fibrosis

HNE, MDA
Vascular Pathologies

- Portal inflow
  - EHPVO
  - Portal Vein Sclerosis

- Hepatic artery pathologies
  - Rare, hepatic artery problems more seen after LTx

- Hepatic venous outflow
  - Budd Chiari Syndrome
  - Sinusoidal obstruction syndrome
Medusa Head venous pattern
Portal hypertension

- Increased pressure in peritoneal capillaries
  - Ascites
- Portosystemic shunting of blood
  - Development of collateral channels
    - Caput medusae
    - Esophageal varices
    - Hemorrhoids
  - Shunting of ammonia and toxins from the intestine into the general circulation
    - Hepatic encephalopathy
- Splenomegaly
  - Anemia
  - Leukopenia
  - Thrombocytopenia

Figure 40-13 Mechanisms of disturbed liver function related to portal hypertension.
Spider Naevi
Renal Involvement In Liver Disease
Pathogenesis of Acute Kidney Injury

Arterial vasodilatation ("VASOPLEGIA")

Decreased SVR → High Cardiac Output

Renal Auto-regulation becomes Pressure Dependent → Intra-renal Vasoconstriction
Aetiology of renal involvement in LD

• Multifactorial
• Hypovolaemia induced pre-renal AKI
• Acute tubular necrosis due to profound hypovolemia and hypotension.
• Direct drug nephrotoxicity (paracetamol, NSAIDs) OR Drugs affecting both liver/kidney
• Hepatorenal syndrome
• Intra-abdominal hypertension (IAH) and development of ICS
HEPATO-RENAL SYNDROME
HRS - Diagnosis of exclusion

• Hepatorenal syndrome (HRS) is defined as the occurrence of renal failure in a patient with advanced liver disease in the absence of an identifiable cause of renal failure.

• The diagnosis of HRS is one of exclusion, so investigations should be performed to rule out other common causes of AKI.
## Characteristics of Type 1 and Type 2 Hepatorenal Syndrome

<table>
<thead>
<tr>
<th></th>
<th>Course</th>
<th>Precipitating Event</th>
<th>History of Diuretic-Resistant Ascites</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type -1 HRS</td>
<td>Precipitous doubling of serum creatinine in &lt; 2 weeks</td>
<td>Present in &gt; 50% of cases</td>
<td>May or may not be present</td>
<td>Without therapy-90-day survival of 10%</td>
</tr>
<tr>
<td>Type -2 HRS</td>
<td>Gradually progressive</td>
<td>Absent</td>
<td>Always Present</td>
<td>Median survival-6 months</td>
</tr>
</tbody>
</table>
Ascites
Intra-abdominal pressure

Sugrue et al Arch Surg 1999 134:1082
Malbrain CCM 2005;33:315

263 patients  40.7% increased IAP
Renal dysfunction:
32% with IAP elevated
14% with normal IAP
32% IAP > 12
40% IAP > 20
HEPATOPULMONARY SYNDROME
HPS and clubbing in CLD
Definition – HEPATOPULMONARY SYNDROME

Arterial Oxygenation Defect induced by intrapulmonary vascular dilatation (IPVD) associated with hepatic disease
Hepatopulmonary syndrome (HPS)

Liver disease

- Shunting & Arterial hypoxemia
- Intrapulmonary Vascular dilatation

*In absence of intrinsic cardiopulmonary disease*
Pathogenesis

- Enhanced pulmonary production of nitric oxide
- Exhaled nitric oxide increased in HPS, normalise after transplant
- Nitric oxide synthesized by nitric oxide synthase – eNO and iNO
  - eNO – pulmonary endothelial cells
  - iNO – alveolar macrophages
- Endothelin 1 acts through ET-A (vascular smooth muscle) or ET-B receptors (pulmonary endothelium)
- ET-A causes vasoconstriction, ET-B causes vasodilatation
Mechanism of hypoxaemia in HPS

A Homogeneous lung

B Hepatopulmonary syndrome
Clinical Features of HPS

- Non-specific
- Dyspnoea at rest/exertion
- Platypnoea/orthodeoxea – Arterial PaO2 decreases by 5% or more when the patient moves from a supine to an upright position - further ventilation-perfusion mismatch
- Spider nevi, digital clubbing, cyanosis
- Differential Diagnosis :
  - Several pulmonary complications or pleural complications
  - Porto-pulmonary hypertension (PPHTN)
CARDIOVASCULAR INVOLVEMENT IN ALF
Cardiovascular changes in ALF - Pathogenesis

- Multi-factorial
- Lesser intake, ongoing losses - hypovolaemia
- Severe SIRS and sepsis play a paramount role.
- Vasodilatation - due to loss of vascular tone leads to systemic hypotension, low effective arterial blood volume and high cardiac output
- Cytokine release from the failing liver appears to be partly responsible for the observed haemodynamic disturbances
- Subclinical myocardial injury
Implication

The associated cardiovascular collapse and organ hypo-perfusion may be central to the progression of multiple organ failure
Strategy

• Target hypovolaemia - fluids
• Target SIRS, infection - antibiotics
• Target vasodilatation – vasopressors- noradrenaline, vasopressin
• If myocardial depression - Inotropes
• Target Adrenal insufficiency
• Optimise oxygen delivery
Neurological Involvement in Liver Disease
Neurologic Support; Brain Swelling

Neurotoxins; ↑ Ammonia

- Astrocytic metabolism to glutamine
  Increased intra-cellular osmotic load

- Mitochondrial toxicity
  Failure of energy metabolism

Neurotransmitter alterations

Systemic Inflammatory Response

Vascular function
- Vasomotor dysfunction
- Endothelial dysfunction

Alterations in BBB?
- Water/neurotoxin permeability

Mitochondrial toxicity
- Failure of energy metabolism

Acute Hepatic Dysfunction
Neurological involvement in ALF

- Highly contentious in ALF
- Concept of Hyperaemia vs Ischaemia
- Risk factors for ICP ??
- Neuro-critical care monitoring –To Bolt or Not to bolt ??
- Role of non/minimally invasive monitoring ??
- Management uncertainties ??????
Who is at risk of raised ICP?

- 25-75% of ALF with Grade iii/iv encephalopathy
- Rapid onset
- High ammonia
- Younger age
- Inotropic support
- RRT
Neurologic Support; Arterial Ammonia and Risk of Cerebral Oedema

ALF Cases, n=165

BERNAL W, ET AL. HEPATOLOGY 2007; 46:1844-52
Why does raised ICP matter

- Compromises CPP
- Transtentorial herniation
- 2nd commonest cause of death in ALF
- Does measuring it help?
Summary

Effects of portal hypertension
- Esophageal varices
- Hematemesis
- Peptic ulcer
- Melena
- Splenomegaly
- Caput medusae
- Ascites
- Hemorrhoids

Effects of liver cell failure
- Coma
- Scleral icterus
- Fetor hepaticus (breath smells like a freshly opened corpse)
- Spider nevi
- Gynecomastia
- Jaundice
- Loss of sexual hair
- Liver "flap" = asterixis (coarse hand tremor)
- Bleeding tendency (decreased prothrombin)
- Anemia
- Testicular atrophy
- Ankle edema

Presentation of cirrhosis/portal hypertension.
Conclusions

Understanding of applied anatomy and physiology is essential to understand the complications and natural history of liver disease.