Pathophysiology of Gallstone Formation and Pancreatitis

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Pancreatic secretions and bile are required for digestion

Bile: Emulsification of fat
Pancreatic secretions: Digestion of proteins, carbohydrates and fat

GALLSTONES

Bile
- Secreted by hepatocytes
- Transported through the biliary system
- Stored and concentrated in the gallbladder
- Released into duodenum after ingestion of food (mediated by CCK)

Bile composition

Bile composition
- Cholesterol
- Bile salts
- Phospholipids
- Miscellaneous (Pigment, Protein)

Formation and secretion of bile acids

1. Synthesis (0.3-0.6g)
   - Cholesterol
   - Cyp7a
   - Bile acids

2. Enterohepatic circulation (5-10x daily)
   - ABCG11
   - ABCG1

Fecal loss 0.3-0.6g
(equals hepatic synthesis)
FXR is bile acid sensor of bile acids and lowers intracellular bile acid levels (to prevent toxicity)

Cholesterol → Cyp7a → Bile acids → FXR → ABCG11

Secretion of cholesterol

Cholesterol → Synthesis → HDL → SR-BI → Export into Periphery (VLDL)

LDL → LDL-R

LXR is a cholesterol sensor and lowers intracellular cholesterol levels

Cholesterol → Cyp7a → Bile acids → LXR

Cholesterol requires bile salts for solubilization

STRUCTURE OF MIXED MICELLES IN BILE

LONGITUDINAL SECTION

CROSS SECTION

Excess cholesterol precipitates to form cholesterol crystals and stones

Composition of Gallbladder bile

Healthy controls

Patients with Gallstones
Cholesterol stones: - Great majority of all stones in the US (>70%) - either pure cholesterol stones or mixed stones (more than 50% cholesterol content)

Pigment stones: - contain pigment = bilirubin - usually due to increased hemolysis - or due to decreased bilirubin conjugation

Factors Favoring Cholesterol Gallstones

• Hepatic Production of Lithogenic Bile
  A. Decreased Secretion of Bile Acids
     1. Fasting (pooling of bile salts in gallbladder)
     2. Decreased bile salt synthesis despite diminished pool
     3. Cyp7a mutations (rare)
     4. Decreased bile acid return to liver (ileal resection)

• Gallbladder Factors
  1. Stasis (TPN, progestins, crash diet)
  2. Nucleation (increased mucoproteins)

Natural History of Gallstones

• 80% of all gallbladder stones will never cause symptoms

• 1-4% of gallbladder stones/year cause symptoms (e.g. colic, pancreatitis)

Factors Favoring Cholesterol Gallstones

• Hepatic Production of Lithogenic Bile
  B. Excess cholesterol secretion
     1. Obesity
     2. Estrogens
     3. Genetic factors/Ethnicity (Pimas)

• Gallbladder Factors
  1. Stasis (TPN, progestins, crash diet)
  2. Nucleation (increased mucoproteins)

Schematic diagram for the management of gallstone disease

- Only if contraindications for surgery:
  - Observation
  - Ursodiol
  - Possibly emergency
**Major functional units**

- **ACINUS**
  - Digestive enzyme secretion

- **DUCTULE**
  - Water, bicarbonate secretion

**HC$_3^-$ concentration and pH increase with increased pancreatic secretion**

<table>
<thead>
<tr>
<th>Ion (mEq/L)</th>
<th>0</th>
<th>0.2</th>
<th>0.4</th>
<th>0.6</th>
<th>0.8</th>
<th>1.0</th>
<th>1.2</th>
<th>1.4</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.0</td>
<td>8.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- The increase in HC$_3^-$ serves to buffer the acidic pH of food after it passes into the duodenum.

**Ion Transport in Duct cells**

- **Na-HCO$_3^-$ Cotransporter**
- **Na-K ATPase**
- **Cl-HCO$_3^-$ Antiport**
- **CFTR (cAMP)**

**Bicarbonate secretion**

- **Cephalic phase**
- **Food cues**

- **Gastric phase**
  - Distention
  - Vagal afferents

- **Intestinal phase**
  - pH-sensitive secretin-releasing factor
  - Secretin
  - H$_2$O, NaHCO$_3^-$

- **Dorsal Vagal Complex**
  - Vagal afferents

- **Vagal efferents**
Regulation of Enzyme Secretion

Pathogenesis of Pancreatitis

Classification of Pancreatitis

Etiology of Acute Pancreatitis

Cellular Injury through Activated Enzymes
Local effects of inflammation and pancreas injury

- Third space losses
- Fat necrosis
- Pancreatic and peripancreatic necrosis

**Cytokines Play an Important Role in Pancreatic Injury**

- Cytokine production
- Inflammation
- Cell Death
- Insult
- Macrophage
- Neutrophil
- Chemoattraction and activation

**Pancreatic Acinar Cell**

- Proinflammatory Microcirculation
  - PAF
  - Endothelin
  - INOS
  - ICAM-1
- TNF-α
- IL-1β
- IL-6

**Etiology of Chronic Pancreatitis**

- Alcoholic
- Cystic fibrosis
- Hereditary pancreatitis
- Hypertriglyceridemia
- Autoimmune
- Fibrocalcinic (Tropical)
- Idiopathic
- Other

**Effects of Chronic Alcohol on the Pancreas**

- Calcification
- Fibrosis
- Decreased blood flow
- Cytotoxic lymphocytes
- Altered protein synthesis
- Direct toxic effects

**Inherited Pancreatitis**

- Mutations in cationic trypsinogen
- Autosomal dominant
- Incomplete penetrance
- Early onset
- Frequent calcification
- Increased pancreatic cancer

**Liver**

- INOS
- ICAM-1
- TNF-α
- IL-1β
- IL-6

**Lungs**

- INOS
- ICAM-1
- TNF-α
- IL-1β
- PAF

**Liver failure**

- Shock, Organ failure
- ARDS
**PANCREATITIS**

**CLINICAL CONSIDERATIONS**

Other causes of hyperamylasemia and hyperlipasemia:

<table>
<thead>
<tr>
<th>Cause</th>
<th>Amylase</th>
<th>Lipase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumors</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Biliary disease</td>
<td>yes</td>
<td>slight</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Renal failure</td>
<td>yes</td>
<td>slight</td>
</tr>
<tr>
<td>Intestinal obstruction, ulceration, ischemia</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Ectopic pregnancy</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Macroamylasemia</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Perforated viscus</td>
<td>yes</td>
<td>yes</td>
</tr>
</tbody>
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**LABORATORY DIAGNOSIS**

Amylase and Lipase are typically highly elevated

**IMAGING DIAGNOSIS**

Interstitial pancreatitis

Necrotizing pancreatitis

Higher rate of complications (bacterial infection, organ failure) and mortality

If CT is performed within 24h of first symptoms, findings may be normal

**PROGNOSIS OF ACUTE PANCREATITIS**

Ranson’s severity score & mortality

<table>
<thead>
<tr>
<th>Admission</th>
<th>During (PVT 24h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 55 years</td>
<td>Met decrease &gt; 10%</td>
</tr>
<tr>
<td>WBC &gt; 16,000 mm$^3$</td>
<td>S 2UN increase &gt; 5 mg/dl</td>
</tr>
<tr>
<td>Glucose &gt; 200 mg/dl</td>
<td>Ca$^2+$ &lt; 8 mg/dl</td>
</tr>
<tr>
<td>LDH &gt; 350 IU/L</td>
<td>PAO$_2$ &lt; 60 mm Hg</td>
</tr>
<tr>
<td>AST &gt; 120 IU/L</td>
<td>Base deficit &gt; 4 mEq/L</td>
</tr>
<tr>
<td>Hct decrease &gt;10%</td>
<td>Negative fluid balance &gt;6L</td>
</tr>
</tbody>
</table>

**Acute Pancreatitis Complications**

Grey-Turner sign

ARDS

Obstructing Pseudocyst

**Acute Pancreatitis Complications**

Infected Necrosis

Treatment

Antibiotic
**PANCREATIC FLUID COLLECTION NOMENCLATURE**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute collection</td>
<td>A.P./ trauma, &lt;48 hrs, no wall</td>
</tr>
<tr>
<td>Pancreatic Necrosis (early)</td>
<td>A.P., 1-2 wks&gt;30 % necr., no wall</td>
</tr>
<tr>
<td>Organized necrosis</td>
<td>A.P., &gt;2-4 wks, partially walled necrotic debris &amp; panc. juice</td>
</tr>
<tr>
<td>Acute pseudocyst</td>
<td>A.P., &gt;4 wks, walled juice</td>
</tr>
<tr>
<td>Chronic pseudocyst</td>
<td>C.P., walled juice/&quot;retention&quot;</td>
</tr>
<tr>
<td>Pancreatic abscess</td>
<td>A.P./C.P./ trauma, peripanc. collection of pus, no debris</td>
</tr>
</tbody>
</table>

Adapted from Bradley et al Atlanta Symposium, Arch Surg 1993 & Baron et al GIE 2002

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**Chronic Pancreatitis: Diagnostic tests**

- **Imaging**
  - ERCP/EUS (Most sensitive)
  - CT (Less sensitive)
  - Abdominal x-ray

- **Functional**
  - Secretin test
  - Fecal chymotrypsin
  - Serum trypsinogen
  - Fecal fat
  - Blood glucose

- **Imaging of Chronic Pancreatitis**
  - Abdominal X-ray
  - Abdominal Ultrasound
  - CT scan
  - ERCP

**Chronic Pain is a Common Symptom of Chronic Pancreatitis**

- Sources of Pain
  - Stenosis of common bile duct
  - Acute inflammation
  - Neural inflammation
  - Inflammation

- Exogenous Proteases degrading CCK-RF
  - CCK-RF cell

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**Amylase and Lipase are often within the normal range!!**