Pathophysiology of Gallstone Formation and Pancreatitis

Robert F. Schwabe
rfs2102@columbia.edu

Pancreatic secretions and bile are required for digestion

- Bile: Emulsification of fat
- Pancreatic secretions: -Digestion of proteins, carbohydrates and fat -Neutralization of the acidic chyme
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 Salts: 12%
- Cholesterol: 4%
- Miscellaneous (Pigment, Protein): 1%
- Water: 84.3%
Bile salts are conjugated with glycine or taurine to increase their solubility at lower pH

Important functions of bile

1. Emulsification of fats in the intestine

2. Cholesterol excretion
   a. Bile salts are generated from cholesterol and their synthesis thus decreases the cholesterol pool
   b. Cholesterol is excreted into bile
Formation and secretion of bile acids

1. Synthesis (0.3-0.6g)

- Cholesterol
  - Cyp7a
  - Bile acids

  Fecal loss 0.3-0.6g
  (equals hepatic synthesis)

2. Enterohepatic circulation (5-10x daily)

  ABC transporters
  Various proteins located at the basolateral membrane that mediate transport of bile acids, cholesterol and phospholipids into bile

  Pool = 2-3g

Why do we have a mechanism for enterohepatic circulation of bile acids?

Reabsorption and redelivery of bile acids allows to very quickly replenish the pool of bile acids in the liver/gallbladder

→ The digestive tract is prepared for the next meal within a relatively short time.
FXR is a sensor of bile acids and prevents bile acid toxicity.

The Nuclear receptors FXR plays an important role in bile salt metabolism.

Increasing bile acid secretion into bile may prevent gallstone formation.

**FXR stimulation:**
1. Decreased bile salt synthesis
2. Increased bile salt secretion

Lowers intracellular bile acid pool.

Increasing bile acid secretion into bile may prevent gallstone formation.

**Secretion of cholesterol**

- Synthesis
- Export into Periphery (VLDL)

HDL
- SR-BI

LDL
- LDL-R

Cholesterol

Bile acids

ABCG5/8

**Bile salts are hepatoxic at high concentrations**
The nuclear receptor LXR is a cholesterol sensor and lowers intracellular cholesterol levels

LXR stimulation:
1. Increased bile salt synthesis decreases cholesterol
2. Increased cholesterol secretion

Cholesterol requires bile salts for solubilization
Excess cholesterol precipitates to form cholesterol crystals and stones

Composition of Gallbladder bile

- Healthy controls
- Patients with Gallstones
Where do gallstone develop?

**Very large stones**
Unlikely to pass into the duct but more likely to cause local problems

**Smaller stones**
Can pass into the duct and cause biliary colic/cholestasis/pancreatitis

**Sludge (viscous aggregate of crystals and mucus)**
Can pass into the duct but is much less likely to cause problems as it can easier pass the papilla

Factors influencing the prevalence of gallstones

**Age**
- under 30y: 1-6%
- 50-60y: 9-30%

**Female gender/ sex hormones**
- Men under 30: 1-3%
- Women under 30: 2-6%
- Men 50-60y: 9-22%
- Women 50-60y: 16-30%

**PREGNANCY**
- 2. Trim: 5.1%
- 3. Trim: 7.9%
- 4-6w pp: 10.2%

**Environmental and genetic factors**
- Female Pima Indians >25y: 73%
- Low prevalence in Asia and Africa
**Cholesterol stones:**
- Great majority of all stones in the US (>80%)
- either pure cholesterol stones or mixed stones (more than 50% cholesterol content)

**Main contributing factors:**
- Decreased bile acids
- Increased biliary cholesterol
- Gallbladder factors allowing for stasis/nucleation

**Supersaturation**

**Pigment stones:**
- much less common in US than Cholesterol stones
- contain pigment = bilirubin

**Main causes**
- Chronic Hemolysis
  - excess bilirubin
- Decreased bilirubin conjugation
  - decreased bilirubin solubility (cirrhosis, bacterial infections)
x-Ray Appearance of Gallstones

<table>
<thead>
<tr>
<th>Radio-opaque</th>
<th>Radiolucent</th>
</tr>
</thead>
<tbody>
<tr>
<td>27% = Cholesterol Stones</td>
<td>83% = Cholesterol Stones</td>
</tr>
<tr>
<td>73% = Pigment Stones</td>
<td>17% = Pigment Stones</td>
</tr>
</tbody>
</table>

Factors Favoring Cholesterol Gallstones

• Hepatic Production of Lithogenic Bile

A. Excess cholesterol secretion
   1. Obesity
   2. Estrogens
   3. Crash diet
   4. Genetic factors/Ethnicity (Pimas) - Point Mutation in ABCA8 accounts probably for 10% of gallstones (Nat. Genetics 2007)
Factors Favoring Cholesterol Gallstones

• Hepatic Production of Lithogenic Bile
  B. Decreased Secretion of Bile Acids
    1. Decreased bile salt synthesis despite diminished pool, e.g.
       Cyp7a mutations (rare)
    2. Decreased bile acid return to liver (ileal resection)

• Gallbladder Factors
  1. Stasis (TPN, fasting, progestins)
  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, cholecystitis)
SUMMARY GALLSTONES

1. Over 80% of gallstones are CHOLESTEROL stones caused by a dysbalance between cholesterol and bile acids in bile

2. FASTING (Gallbladder stasis), OBESITY (increased cholesterol secretion) and ESTROGEN (increased cholesterol secretion) promote gallstone formation

3. SMALLER GALLSTONE pass easier into the duct

4. 80% of gallstones remain unsymptomatic

5. Therapy of choice for symptomatic gallstone disease is laparoscopic cholecystectomy
PANCREAS PHYSIOLOGY

Pancreas macro- and microanatomy

- Gall bladder
- Common bile duct
- Pancreas
- Pancreatic duct
- Duodenum
- Duct
- Acini
- Islet of Langerhans
- Delta cell
- Alpha cell
- Beta cell
- Pancreatic acini
- PP cell
- Vessel/RBC
Major functional units

**ACINUS**
Digestive enzyme secretion
(Trypsin, Elastase, Amylase, Lipase)

**DUCTULE**
Water, bicarbonate secretion

---

**HC\(_2\)O\(_3\) concentration and pH increase with increased pancreatic secretion**

The increase in HC\(_2\)O\(_3\) serves to buffer the acidic pH of food after it passes into the duodenum.

Meal-stimulated secretion

![Graph showing secretory rate (ml/min) vs. HC\(_2\)O\(_3\) concentration and pH](image-url)
Bicarbonate secretion is regulated through hormonal and neural mechanisms

**Cephalic phase**
- Food cues

**Gastric phase**
- Distention

**Intestinal phase**
- pH sensitive Secretin-releasing factor
- Secretin S-cells
- Duodenal pH < 4.5

Regulation of Enzyme Secretion is mediated by Neural Mechanisms

**Cephalic phase**
- Food cues

**Gastric phase**
- Distention

**Intestinal phase**
- CCK-sensing Vagal Afferents
- CCK-sensing Vagal Efferents
- Proteins, AA, FA
- CCK-RF
- CCK (I-cells)

Dorsal Vagal Complex

Vagal Afferents

Vagal Efferents

Ach

Secretin

H₂O, NaHCO₃

CFTR

Digestive Enzymes

Ach, VIP, GRP

M3-R
Activation of pancreatic enzymes in the intestine

2 Mechanisms to prevent autodigestion:
- Trypsinogen activation occurs outside of the pancreas
- Pancreatic inhibitor prevents trypsinogen activation

PATHOGENESIS OF PANCREATITIS

Activation of pancreatic enzymes within the pancreas and the resulting autodigestion is the most important mechanism that triggers pancreatitis
Classification of pancreatitis

Functional and morphologic changes

- **CHRONIC**
  - EtOH
  - Outcome:
    - Pain
    - Endocrine insufficiency
    - Exocrine insufficiency

- **ACUTE RECURRENT**
  - e.g. sludge, SOD
  - Outcome:
    - Recovery or death

- **ACUTE**
  - e.g. stone, EtOH
  - Outcome:
    - Recovery or death

Acute Pancreatitis

- Clinically severe
- Typically starts with moderate to severe abdominal pain
- Complications such as pancreatic necrosis, infection, shock and multi-organ failure develop in some patients
Etiology of Acute Pancreatitis

- Autoimmune
- Drug-induced
- Iatrogenic
- IBD-related
- Infectious
- Inherited
- Metabolic
- Neoplastic
- Structural
- Toxic
- Traumatic
- Vascular

Alcoholic

Idiopathic

Other

Biliary

Cellular Injury through Activated Enzymes

1. Blockage of Secretion
2. Activation of Zymogens in Lysosomes (Cathepsin B)
3. Organelle Damage and Cell Injury by Activated Enzymes

Increased pressure
Perturbed environment
Cytokines Play an Important Role in Pancreatic Injury

Cytokines Mediate Systemic Complications

Liver failure

ARDS

Lungs

Shock, Organ failure

Microcirculation

PNFα

IL-1β

TNFα

PAF

ICAM-1

Proinflammatory

INOS

Endothelin

Liver

Pancreatic Acinar Cell

Insult

Cytokine production

Systemic complications

Chemoattraction and activation

Neutrophil

Macrophage

Inflammation

Cell Death

TNFα

IL-1β

IL-61

ICAM-1

ARDS
Local effects of inflammation and pancreas injury

- Pancreatic and peripancreatic necrosis
- Fat necrosis
- Fluid loss into third space

Chronic Pancreatitis

- Chronic disease
- Pain and malabsorption are the main symptoms
- Weight loss can also be due to food avoidance
Etiology of Chronic Pancreatitis

- Alcoholic
- Idiopathic
- Other

- Cystic fibrosis
- Hereditary pancreatitis
- Hypertriglyceridemia
- Autoimmune
- Fibrocalcific (Tropical)

Effects of Chronic Alcohol on the Pancreas

- Calcification
- Fibrosis
- Decreased blood flow
- Direct toxic effects
- Altered protein synthesis (unfavorable ratio of trypsinogen vs. inhibitors)
Hereditary Pancreatitis

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

PANCREATITIS
CLINICAL CONSIDERATIONS
Laboratory parameters are crucial to establish the diagnosis of acute pancreatitis. Amylase and Lipase are typically highly elevated in Acute Pancreatitis. Parotitis is another cause of hyperamylasemia and hyperlipasemia, although Lipase is more specific than Amylase and remains elevated for a longer period.

<table>
<thead>
<tr>
<th>Other causes of hyperamylasemia and hyperlipasemia:</th>
<th>Amylase</th>
<th>Lipase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parotitis</td>
<td>yes</td>
<td>no</td>
</tr>
<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>
</table>

IMAGING DIAGNOSIS is important to judge severity and clinical course of pancreatitis. If CT is performed within 24h of first symptoms, necrosis may not yet be present. Higher rate of complications (bacterial infection, organ failure) and mortality.
PROGNOSIS OF ACUTE PANCREATITIS

Ranson’s severity score & mortality

Admission
- Age > 55 years
- WBC > 16,000 mm³
- Glucose > 200 mg/dl
- LDH > 350 IU/L
- AST > 120 IU/L

During first 48h
- Hct decrease >10%
- BUN increase > 5 mg/dl
- Ca²⁺ < 8 mg/dl
- PaO₂ < 60 mm Hg
- Base deficit > 4 mEq/L
- Negative fluid balance > 6L

Most patients with severe pancreatitis

Acute Pancreatitis Complications

Grey-Turner sign
Cullen sign
ARDS
Obstructing Pseudocyst
No epithelial lining
Acute Pancreatitis Complications

Infected Necrosis

Treatment

Antibiotic

Chronic Pancreatitis: Diagnostic relies on imaging and functional tests

x-ray and fecal fat have a low sensitivity to detect CP!

Amylase and Lipase are often within the normal range!!
Chronic Pancreatitis: Diagnostic tests

### Imaging
- ERCP/EUS
- CT Ultrasonogram
- 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 and Malabsorption/Malnutrition are the most common Symptoms of Chronic Pancreatitis

Exogenous proteases may not only improve maldigestion but also CCK release and pain in chronic pancreatitis
# SUMMARY PANCREATITIS

1. ACUTE PANCREATITIS is a clinically severe disease mostly caused by EtOH and GALLSTONES

2. CHRONIC PANCREATITIS causes pain and malabsorption and is most commonly caused by EtOH

3. The diagnosis of ACUTE PANCREATITIS (but not CHRONIC Pancreatitis) is best made by detection of elevated AMYLASE and LIPASE

4. Imaging (e.g. CT) can reveal severity of acute pancreatitis (interstitial vs. necrotic)

5. CHRONIC PANCREATITIS is diagnosed by imaging (x-Ray, Ultrasound, CT, ERCP) or functional tests (secretin, fecal fat)