Pathophysiology of Gallstone Formation and Pancreatitis

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- Gallbladder/Bile and Pancreas both are essential for digestion of food

- A large percentage of the population have gallstones (up to 30% of people >50y) and about 700000 surgeries and $6 billion cost/year in the US

- Gallbladder and Pancreas physiology are linked as gallstones cause a large percentage of acute pancreatitis cases
Pancreatic secretions and bile are required for digestion.

- Bile: Emulsification of fat
- Pancreatic secretions: -Digestion of proteins, carbohydrates and fats -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** (Lecithin) 12%
- Phospholipids 4%
- **Cholesterol** 8%
- Miscellaneous (Pigment, Protein) 1%
- **H₂O** 84.3%
Bile salts are conjugated with glycine or taurine to increase their solubility at lower pH.

Primary bile salts

- Cholate
- Chenodeoxycholate

Bacterial Dehydroxylation

Secondary bile salts

- Deoxycholate
- Lithocholate
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
  - ABCG11

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

Fecal loss 0.3-0.6g
(equals hepatic synthesis)
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 toxicity. The nuclear receptors FXR in bile salt metabolism play an important role at high concentrations of bile salts.

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

Increasing bile acid secretion into bile may prevent gallstone formation.
Secretion of cholesterol

- HDL
  - SR-BI
- LDL
  - LDL-R

Synthesis

Cholesterol

- Export into Periphery (VLDL)
- Bile acids

- ABCG5/8
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

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Prevalence 1-3%</th>
<th>Trim 2.</th>
<th>Trim 3.</th>
<th>4-6w PP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men under 30</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women under 30</td>
<td>2-6%</td>
<td>2. Trim</td>
<td>3. Trim</td>
<td>4-6w PP</td>
</tr>
<tr>
<td>Men 50-60y</td>
<td>9-22%</td>
<td>5.1%</td>
<td>7.9%</td>
<td>10.2%</td>
</tr>
<tr>
<td>Women 50-60y</td>
<td>16-30%</td>
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## Environmental and genetic factors
- Female Pima Indians >25y: 73%
- Low prevalence in Asia and Africa

## Obesity
- Non-obese women: 10%
- Obese women: 30%
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

<table>
<thead>
<tr>
<th>Cause</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic Hemolysis</td>
<td>excess bilirubin</td>
</tr>
<tr>
<td>Decreased bilirubin conjugation</td>
<td>decreased bilirubin solubility</td>
</tr>
<tr>
<td>(cirrhosis, bacterial infections)</td>
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</tr>
</tbody>
</table>

![Image of pigment stones with scale bar 1 cm]
x-Ray Appearance of Gallstones

Radio-opaque

27% = Cholesterol Stones
73% = Pigment Stones

Radiolucent

83% = Cholesterol Stones
17% = Pigment Stones
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)

![Ultrasound](image1)

**Ultrasound**

![Dilated Duct](image2)

**Dilated Duct**

**Intraductal stone (not always visible)**

![ERCP](image3)

**ERCP**
Gallstones

Schematic diagram for the management of gallstone disease

Asymptomatic

Endoscopic retrograde cholangiopancreatography (ERCP)

Follow-up

Laparoscopic cholecystectomy +/- ERCP

Symptomatic

Uncomplicated

Cholecystectomy

If contraindications for surgery:

- Observation
- Ursodiol
- Possibly emergency surgery

Good success with small cholesterol stones

Very high recurrence rate

- Visualize biliary tree and pancreatic ducts
- Extract stones
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 and are more likely to cause symptoms (colic, pancreatitis, cholecystitis).

4. 80% of gallstones remain unsymptomatic.

5. Therapy of choice for symptomatic gallstone disease is laparoscopic cholecystectomy.
PANCREAS PHYSIOLOGY
Pancreas macro- and microanatomy
Major functional units

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

DUCTULE
Water, bicarbonate secretion
**HC0₃ concentration and pH increase with increased pancreatic secretion**

The increase in HC0₃ serves to buffer the acidic pH of food after it passes into the duodenum.

**Meal-stimulated secretion**

- **Ion (mEq/L)**
  - Na⁺
  - pH
  - HCO₃⁻
  - Cl⁻
  - K⁺

- **pH**
  - 8.0
  - 7.0

- **Secretory rate (ml/min)**
  - 0
  - 0.2
  - 0.4
  - 0.6
  - 0.8
  - 1.0
  - 1.2
  - 1.4
Bicarbonate secretion is regulated through hormonal and neural mechanisms.

**Cephalic phase**
- Food cues

**Gastric phase**
- Distention

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

- Secretin-releasing factor activates S-cells
- S-cells stimulate the release of Secretin
- Secretin stimulates the release of CFTR
- CFTR facilitates the transport of H₂O, NaHCO₃

**Neural mechanisms**
- Vagal Afferents
- Dorsal Vagal Complex
- Vagal Efferents
- Ach (Acetylcholine)
Regulation of Enzyme Secretion is mediated by Neural Mechanisms

Cephalic phase
Food cues

Gastric phase
Distention

Intestinal phase
CCK-RF → CCK (I-cells)
Proteins, AA, FA

Dorsal Vagal Complex
Vagal Efferents
Ach, VIP, GRP

CCK-sensing Vagal Afferents

M3-R

Digestive Enzymes
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

- • Alcoholic
- • Biliary
- • Idiopathic
- • Other

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

S.N.S.
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

Lysosome

Golgi Complex

RER
Cytokines Play an Important Role in Pancreatic Injury

- Insult
  - Pancreatic Acinar Cell
  - Cytokine production
    - Chemoattraction and activation
      - Neutrophil
      - Macrophage
    - Inflammation
    - Cell Death
    - Systemic complications
Cytokines Mediate Systemic Complications

Liver failure

Liver

Liver failure

TNFα
IL-1β
IL-61

ARDS

Lungs

Shock, Organ failure

Microcirculation

ICAM-1
IL-1β
TNFα
PAF

Proinflammatory

PAF
Endothelin
INOS
ICAM-1
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
- Cytotoxic lymphocytes
- 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

Spink

[Genetic tree diagram showing affected individuals]
PANCREATITIS
CLINICAL CONSIDERATIONS
Laboratory parameters are crucial to establish the diagnosis of acute pancreatitis.

Lipase is more specific than Amylase and remains elevated for a longer period.

Other causes of hyperamylasemia and hyperlipasemia:

<table>
<thead>
<tr>
<th>Condition</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.
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

**Systemic disease**

**Causative Treatment:**
- Stone extraction in severe biliary pancreatitis
- (Cessation of Alcohol intake)

**Supportive Treatment:**
- Enteral feeding (nasogastric tube)
- Intravenous hydration
- Pain medication
- Intubation in case of respiratory problems
Acute Pancreatitis Complications

Grey-Turner sign

Cullen sign

ARDS

No epithelial lining

Obstructing Pseudocyst
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)