Pathophysiology of pancreatitis and gallstone formation

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PANCREAS PHYSIOLOGY

Major functional units

ACINUS
Digestive enzyme secretion

DUCTULE
Water, bicarbonate secretion

Regulation of Bicarbonate Secretion
Duodenal pH < 4.5 (intestinal phase)
Vagal Afferents
Dorsal Vagal Complex
Vagal efferents

Duodenal pH < 4.5 (intestinal phase)

Distention (gastric phase)
Food cues (cephalic phase)

pH sensitive Secretin-releasing factor
Secretin release by duodenal S cells

ACH
DAG/IP3

Acetylcholine (neural) secretin (tumoral)

SECRETIN

CAMP

DUCTAL CELL PHYSIOLOGY

Duct cell model

Na-HCO3 Cotransporter
Na-K ATPase

Na, K, H2O
Basolateral
Luminal

H2O + CO2
HCO3

Na
Cl

CFTR (cAMP)
Regulation of Enzyme Secretion

CCK from I cells (intestinal phase)
Vagal Afferents
Dorsal Vagal Complex
Vagal efferents

ACH, GRP, CCK
DAG/IP3

Food cues (cephalic phase)

Distention (gastric phase)

FA AA Proteins
(intestinal phase)

CCK-RF Monitor peptide

Classification of pancreatitis

Functional and morphologic changes

CHRONIC
e.g. ETOH, hereditary
Outcome:
Pain
Endocrine insufficiency
Exocrine insufficiency

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

ACUTE
e.g. stone, drug, toxin
Outcome:
Recovery or death

Acute Pancreatitis

Etiologies

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

Acute Pancreatitis

PATHOGENESIS OF PANCREATITIS

Intracellular Injury
- Sloughing of acinar
- Fusion of acinar zymogen
- and amylase
- Activation of enzymes
- Intracellular injury

Duct Pressure
Toxin

PATHOGENESIS OF PANCREATITIS
**Model for Inflammatory and Acinar Cell Death Responses in Pancreatitis**

- Insult
- Cytokine production
- Chemoattraction and activation
- Chemoattraction and migration
- Regulation of cell death
- Neutrophil/Monocyte
- Macrophage

**Etiology of chronic pancreatitis**

- **Alcoholic**
- **Hereditary pancreatitis**
- **Cystic fibrosis**
- **Hypertriglyceridemia**
- **Autoimmune**
- **Fibrocalcific (Tropical)**
- **Idiopathic**

**Hereditary Pancreatitis**

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

Conditions Associated with Hyperamylasemia and Hyperlipasemia
- Parotitis
- Tumors
- Acute pancreatitis
- Chronic pancreatitis
- Acute cholecystitis
- Acute hepatitis
- Cystic disease
- Ruptured pseudocyst
- Pancreas divisum
- Pancreatic pseudocyst
- Pancreatic necrosis
- Acute collection

DIAGNOSIS

CT without IV contrast
- Mild acute pancreatitis
- Severe acute pancreatitis

CT with IV contrast
- Interstitial pancreatitis
- Necrotizing pancreatitis

PROGNOSIS OF ACUTE PANCREATITIS
Ranson’s severity score & mortality

<table>
<thead>
<tr>
<th>Admission</th>
<th>After 48 hrs</th>
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<tbody>
<tr>
<td>Age &gt; 55 years</td>
<td>Hematocrit decrease &gt; 10%</td>
</tr>
<tr>
<td>WBC &gt; 16,000 mm³</td>
<td>BUN increase &gt; 5 mg/dl</td>
</tr>
<tr>
<td>Glucose &gt; 200 mg/dl</td>
<td>Ca²⁺ &lt; 8 mg/dl</td>
</tr>
<tr>
<td>LDH &gt; 350 IU/L</td>
<td>Base deficit &gt; 4 mEq/L</td>
</tr>
<tr>
<td>AST &gt; 120 IU/L</td>
<td>Negative fluid balance &gt; 6L</td>
</tr>
</tbody>
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Most patients with severe pancreatitis

Acute Pancreatitis Complications
- Grey-Turner sign
- ARDS
- Obstructing Pseudocyst
- Necrotizing pancreatitis

Pancreatic Fluid Collection Nomenclature

<p>| | |</p>
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Acute collection</td>
<td>A.P./ trauma, &lt;48 hrs, no wall</td>
</tr>
<tr>
<td>Pancr. Necrosis (early)</td>
<td>A.P., 1-2 wks: ≥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
Infected Pancreatic Necrosis

**Diagnosis**

- ERCP (EUS)
- CT scan
- Ultrasoundogram
- Abdominal x-ray

**Treatment**

- ERCP
- CT scan
- Ultrasound

Calcific Chronic Pancreatitis

**Tests**

- ERCP (EUS)
- CT scan
- Abdominal x-ray

**Function**

- Secretin test
- Serum tryptase
- Fecal chymotrypsin

Exogenous Proteases degrading CCK-RF

Exogenous Proteases may decrease CCK release and pain in chronic pancreatitis

List of images:

- Infected Pancreatic Necrosis Diagnosis and Treatment
- Sources of Pain
- Calcific Chronic Pancreatitis Tests and Function
- Relationship Between Lipase Output and Steatorrhea
GALLSTONES

AVERAGE COMPOSITION OF NORMAL GALLBLADDER BILE

Per Cent by Weight

Phospholipids 4% (>95% Lecithin)
Cholesterol 0.7% (non-esterified)
Miscellaneous <1% (Bile pigment, inorganic electrolytes, and protein)

WATER 82.3%

Bile Salts 12%

STRUCTURE OF MIXED MICELLES IN BILE

LONGITUDINAL SECTION

CROSS SECTION

Lecithin
Bile Salts
Cholesterol
Polar Groups

X-RAY APPEARANCE OF GALLSTONES

RADIO-OPAQUE

27% = CHOLESTEROL STONES
73% = PIGMENT STONES

RADIOLUCENT

83% = CHOLESTEROL STONES
17% = PIGMENT STONES

BILE SALT KINETICS IN MAN
(5-7 Day Steady-state Studies)

HEPATIC SYNTHESIS
0.3-0.6g/day

POOL 2.3g CIRCULATES 5-10x daily

HEPATIC SECRETION RATE
15-30g/day

FECAL EXCRETION
[SYNTHESIS RATE] 0.3-0.6g/day
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)
Factors Favoring Cholesterol Gallstones

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

• Gallbladder Factors
  1. Stasis (TPN, progestins, crash diet)
  2. Nucleation (increased mucoproteins)
  3. Infection (deconjugation of bilirubin)
  2. Effect of removing the gallbladder