Relationship Between Exocrine and Endocrine Pancreas

Makoto Otsuki, MD, PhD

Department of Gastroenterology and Metabolism, University of Occupational and Environmental Health, Japan, School of Medicine
The Pancreas

is usually regarded as two separate organ systems.

The exocrine pancreas
accounts for about 85% of the volume of the pancreas

The endocrine pancreas
• accounts for 1 to 2% of the volume of the pancreas
• about 1 million islets in the pancreas
• the islets contain 4 major types of endocrine cells
• the islet is composed of about 5,000 endocrine cells
Endocrine and Exocrine Pancreas are closely linked both anatomically and physiologically.

Secrete hormones into the bloodstream

Secrete digestive enzymes, water and bicarbonate into the duodenum

Secrete hormones into the blood stream
The exocrine pancreas receives a large part of its blood flow through the islets and is therefore exposed to high concentrations of islet hormones.
Effect of Hypoinsulinemia on the Exocrine Pancreas
Diabetes Mellitus Often Associates Exocrine Pancreatic Abnormalities

Morphological Alterations

1. Reduction of pancreatic size (US and CT images)
2. Changes of pancreatic duct system by ERCP
3. Histological changes; acinar atrophy, fibrosis, fatty degeneration

Functional Alterations

1. Reduced serum and fecal pancreatic enzyme levels
2. Reduced secretagogue-stimulated secretion
3. Reduced enzyme content in the pancreas

- Lack of trophic hormone (insulin)
- High level of inhibitory hormone (glucagon, somatostatin)
- Inadequate perfusion of the exocrine pancreas (atherosclerosis)
The pancreas is smaller in DM patients than in control subjects. The reduction in size is more pronounced in type 1 DM than in type 2 DM.

The body of the pancreas is significantly reduced in all three groups.

Size of the pancreas in patients with type 2 DM who require insulin therapy is nearly the same as that in patients with type 1 DM.

AJR 159:527-531, 1992
Relationship between FPG and Serum Amylase Activity in Patients with Type 2 DM

![Graph showing the relationship between FPG and Serum Amylase Activity. The x-axis represents FPG (mg/100ml) with categories: <120, 120-159, 160-199, ≥200. The y-axis represents Amylase Activity (SU/100ml) with categories: 0, 40, 60, 80, 100, 120, 140, 160, 180, and 200. The graph displays the distribution of data points for each category.]

- FPG categories: <120, 120-159, 160-199, ≥200
- Amylase Activity categories: 0, 40, 60, 80, 100, 120, 140, 160, 180, 200

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**Legend:**
- Green dots represent data points.
- White lines indicate the boundaries of each FPG category.
Pancreatic Exocrine Function in Patients with Type 2 DM -CCK-Secretin Test-

- Maximum Bicarbonate (mEq/L)
  - Control: 100, Diabetics: n.s.

- Total Volume (ml/kg BW)
  - Control: 3, Diabetics: n.s.

- Amylase Output (SU/kg BW)
  - Control: 6000, Diabetics: p<0.02
Relationship between FPG Concentrations and Serum Immunoreactive Trypsin Levels

![Graph showing the relationship between FPG concentrations and serum immunoreactive trypsin levels. The graph indicates statistically significant differences at P<0.05 between different FPG concentration groups.](image)
Relationship between HbA1c and Serum Immunoreactive Trypsin Levels

IR-Trypsin (ng/ml)

<table>
<thead>
<tr>
<th>HbA1c (%)</th>
<th>Control</th>
<th>&lt;7.0</th>
<th>7.0-7.9</th>
<th>8.0-8.9</th>
<th>9.0</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>70</td>
<td>60</td>
<td>60</td>
<td>70</td>
<td>80</td>
</tr>
</tbody>
</table>

# P<0.05 vs control
Serum levels of amylase and trypsin were inversely related to fasting plasma glucose concentration. Decrease in serum trypsin concentration was related to poor glycemic control.
Relationship Between the Severity of Diabetes Mellitus and Exocrine Pancreatic Dysfunction

(A) Blood Glucose  (B) Insulin Content  (C) Amylase Content

Blood Glucose (mg/dl)

- 60 mg
- 45 mg
- 30 mg
- Control

IRI Content (μg/mg protein)

- STZ (mg/Kg BW)
  - 30 mg
  - 45 mg
  - 60 mg

Amylase Content (SU/mg protein)

- STZ (mg/Kg BW)
  - 30 mg
  - 45 mg
  - 60 mg

P-values:

- P<0.001
- P<0.001
- P<0.001
- P<0.005
- n.s.
- P<0.005
- n.s.
Effect of Hyperinsulinemia on the Exocrine Pancreas
• Since there are no significant capsule or basement membrane around the islets, acinar tissue in the pancreas is in close contact with the islets.

• Acinar cells near the islets, peri-islet acini, are larger, contain larger nuclei and nucleoli, and have more abundant zymogen granules than other acini.

• These characteristics are related to local high insulin levels.
There are no reports that revealed increased functional activity of the exocrine pancreas at hyperinsulinemic and normoglycemic state.
Effect of Exogenous and Endogenous Insulin on CCK-Induced Exocrine Secretion

(A) Exogenous Insulin

(B) Endogenous Insulin

Exocrine Pancreatic Function in Patients with Insulin-Producing Tumors

- Marked and significant decrease in zymogen granule content in acinar cells.
- Slight reduction in the mean cell area.
- Increase in centroacinar/ductular cell area and cell number.
- No significant difference in the zymogen granule content between peri- and tele-insular acini.

Endocrine Pancreatic Function in Rat with Insulin-Producing Tumors

- Insulinoma-bearing pancreas

- Control
Exocrine Pancreatic Function in Rat with Insulin-Producing Tumors

**Graphs:**
- **Amylase Output (SU/10 min):**
  - Insulinoma-bearing pancreas
  - Control pancreas
- **Flow Rate (µl/10 min):**
- **Total Amylase Output (SU/20 min):**
  - Control
  - Insulinoma-bearing pancreas

**Cerulein:** 0.1 ng/ml

**Glucose:** (mM)
- 2.8
- 8.3

**P < 0.05**

*Dig Dis Sci 29 (5): 443-7, 1984*
Effect of Tumor Removal on Endocrine Pancreatic Function in Rat with Insulin-Producing Tumors

- Insulinoma-bearing pancreas
- Tumor Removal

Glucose (mg/100ml) and Caerulein (0.1ng/ml) with Mean ± SEM

Insulin (ng/ml) vs. Minutes

Controls (n=10) vs. (n=7)
Effect of Tumor Removal on Endocrine Pancreatic Function in Rat with Insulin-Producing Tumors

Graph showing the effect of tumor removal on insulin levels. The graph compares insulin levels (ng/ml) before and after tumor removal. The x-axis represents time, and the y-axis represents insulin levels. The graph shows a significant increase in insulin levels post-tumor removal, indicated by a p-value of <0.05.
Effect of Chronic Pancreatitis on the Endocrine Pancreas

Chronic pancreatitis causes pancreatic fibrosis and sometimes results in diabetes mellitus.
Pancreatogram and Histology of Chronic Pancreatitis
### Pancreatic Tissue Pressure in Chronic Pancreatitis

<table>
<thead>
<tr>
<th>Tissue Pressure (mmHg)</th>
<th>Head</th>
<th>Body</th>
<th>Tail</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference (n=4)</td>
<td>19±5</td>
<td>13±6</td>
<td>11±3</td>
</tr>
<tr>
<td>CP (n=17)</td>
<td>257±59*</td>
<td>201±51*</td>
<td>161±161*</td>
</tr>
</tbody>
</table>

Three to six recordings were obtained at each site. In chronic pancreatitis the pressure (mean +/- s.e.m.) was substantially elevated in all regions of the pancreas compared with reference subjects.

Effect of Intensity and Duration of Pressure on PSC Proliferation

(A) Intensity

(B) Duration

Data are means ± SD. * P<0.0001 vs control
Effect of Pressure on PSC Activation

After the application of pressure at 80 mmHg for 60 min, the level of α-SMA protein was analyzed by Western blot.
Effect of Pressure on Collagen type I mRNA Expression and Collagen Secretion by PSCs

After the application of pressure at 80 mmHg for 60 min.

Collagen secretion into culture medium during 48 h of incubation after pressure
Pressure activates rat PSCs and stimulates type 1 collagen secretion.

Increase of pancreatic tissue pressure further accelerates the development of pancreatic fibrosis via proliferation and activation of PSCs in chronic pancreatitis.
Microcirculation in Alcoholic Chronic Pancreatitis

(A) Normal Pancreas

(B) Chronic Pancreatitis

Blood flow in chronic pancreatitis is significantly lower than that in the corresponding area of the normal pancreas.
Effect of Hypoxia on PSC Activation
-Expression of \( \alpha \)-SMA-

**Control**
- Culture 24h
- Culture 48h

**Hypoxia**
- Culture 24h
- Culture 48h
Effect of Hypoxia (3% O₂) on PSC Proliferation and Activation

(A) BrdU Incorporation

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Hypoxia 24 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>BrdU (% of control)</td>
<td>100</td>
<td>200</td>
</tr>
</tbody>
</table>

P < 0.05

(B) α-SMA Expression

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Hypoxia 24 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expression (% of control)</td>
<td>100</td>
<td>200</td>
</tr>
</tbody>
</table>

P < 0.05
Effect of Hypoxia on Collagen type I mRNA Expression and Collagen Secretion by PSCs

- Relative mRNA Expression of Collagen I
  - Control: 0.2
  - Hypoxia: 8
  - Hypoxia shows a significant increase compared to Control (*P<0.01*)

- Collagen Secretion (mg/ml)
  - Control: 20
  - Hypoxia: 25
  - Hypoxia shows a significant increase compared to Control (*P<0.01*)

24 h
Chronic Pancreatitis

Tissue Pressure

Micro-circulation

Hypoxia

Activation of PSCs

Progression of Pancreatic Fibrosis

Exocrine Insufficiency

Endocrine Insufficiency
Endocrine Pancreatic Function in Patients with Chronic Pancreatitis

![Bar chart showing C-peptide levels in different stages of chronic pancreatitis]

- **Basal C-peptide**
- **△ C-peptide**

- **Control** (19)
- **Normal** (6)
- **Moderately** (14)
- **Severely** (10)

**Exocrine Function in CP**

- #: P<0.001 vs control

Endocrine Pancreatic Function in Patients with Chronic Pancreatitis

Lipase Output-------SC test
ΔC Peptide Value--Glucagon test

r = 0.72  P<0.001


Endocrine Pancreatic Function in Patients with Chronic Pancreatitis

Lipase Output-------SC test
ΔC Peptide Value--Glucagon test

r = 0.72  P<0.001

Prevalence of Diabetes Mellitus during an 8-year Follow-up Study of Patients with Chronic Pancreatitis
Prevalence of Diabetes Mellitus in Patients with Chronic Pancreatitis

1994
- DM (+): 35.1% (n=230)
- DM (-): 63.7% (n=418)
- Unknown: 1.2% (n=8)

2002
- DM (+): 50.4% (n=331)
- DM (-): 47.9% (n=314)
- Unknown: 1.7% (n=11)
# Diabetes Mellitus in Patients with Chronic Pancreatitis

<table>
<thead>
<tr>
<th>Year</th>
<th>DM (+)</th>
<th>DM (-)</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>1994</td>
<td>35.1%</td>
<td>68.7%</td>
<td>2.4%</td>
</tr>
<tr>
<td>(n=230)</td>
<td>(n=418)</td>
<td>(n=10)</td>
<td></td>
</tr>
<tr>
<td>2002</td>
<td>90.0% (n=207)</td>
<td>10.0% (n=23)</td>
<td>12.5% (n=1)</td>
</tr>
<tr>
<td></td>
<td>28.9% (n=121)</td>
<td>68.7% (n=287)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>37.5% (n=3)</td>
<td>50.0% (n=4)</td>
<td></td>
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</tbody>
</table>

Chronic Pancreatitis (n=656)
# Incidence of Diabetes Mellitus in Patients with Newly Diagnosed Chronic Pancreatitis

Newly diagnosed chronic pancreatitis in 1994 without diabetes

<table>
<thead>
<tr>
<th>Year</th>
<th>Chronic Pancreatitis (n=77)</th>
<th>Surgery (+) 35.1% (n=27)</th>
<th>Surgery (-) 64.9% (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1994</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td>Surgery (-) 64.9% (n=50)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>DM (+) 18.0% (n=9)</td>
<td>DM (-) 78.0% (n=39)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unknown 4.0% (n=2)</td>
<td>Unknown 7.4% (n=2)</td>
<td></td>
</tr>
<tr>
<td>2002</td>
<td>DM (+) 37.0% (n=10)</td>
<td>DM (-) 55.6% (n=15)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unknown 7.4% (n=2)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Newly diagnosed chronic pancreatitis in 1994 without diabetes
Incidence of Diabetes Mellitus in Patients with Newly Diagnosed Chronic Pancreatitis without Diabetes

In 1994 0% (77)

In 2002 24.7% (19)

Medical Rx 18% (10)
Surgical Rx 37% (9)
Diabetes mellitus was newly found in 28.9% (121/418) of patients with chronic pancreatitis who were NGT in 1994.

Diabetes mellitus was found in 24.7% (19/77) of patients with newly diagnosed chronic pancreatitis who were NGT in 1994.
Autoimmune Pancreatitis

Unique form of Chronic Pancreatitis characterized by infrequent attacks of abdominal pain, swelling of the pancreatic parenchyma, and diffuse irregular narrowing of the main pancreatic duct (MPD).
Exocrine Pancreatic Function in AIP

Secretin Test was performed in 10 patients with AIP and was abnormal in all of them.

PABA Excretion (%)

- Abnormally low in 81% patients (29/36) with AIP.
- Pancreatic exocrine function is sometimes impaired.

BT-PABA Test

Secretin Test was performed in 10 patients with AIP and was abnormal in all of them.
Diabetes Mellitus in Patients with AIP
(Definite AIP 167)

Diabetes Mellitus 66.5%

Type 1 DM 4%
Type 2 DM? 53%
DM type? 9%
DM (-) 33.5%

(n=167)
Diabetes Mellitus in Patients with AIP

Onset of DM in Relation to AIP

( Definite AIP 93 )

Before AIP 33%
With AIP 52%
After PSL Rx 14%
After Px 1%

Although DM appeared after steroid therapy in 14%, DM was diagnosed before or simultaneously with the diagnosis of AIP in 85%. Treatment with steroids improved DM in some patients.
Following steroid therapy, the pancreas became small and atrophic suggesting that AIP is a progressive disease and that AIP is a possible early stage of idiopathic chronic pancreatitis.
Effect of Hyperglycemia on the Exocrine Pancreas
Effects of Glucose Loading on Serum Amylase Activity

(A) Per oral

(B) Intravenous

Serum Amylase

Plasma Glucose

Time (min)

Serum Amylase

Plasma Glucose

Time (min)
Relationship Between Plasma Glucose Levels and Serum Pancreatic Amylase Activity

\[ r = 0.458 \]
\[ p < 0.05 \]

Pancreatic-type Amylase (\%) vs. Plasma Glucose (mg/100ml)

\[ y = 116.5 - 0.56x \]
Effect of High Glucose Concentration on Pancreatic Stellate Cells
Effect of Glucose Concentration on PSC Proliferation and Activation

(A) PSC Proliferation

(B) \(\alpha\)-SMA Expression

\[ p < 0.05 \]

Glucose (mM) 5.6 25.2 33.6

PSC Proliferation (OD)

\[ p < 0.05 \]

\(\alpha\)-SMA Expression (Densitometer units (% of control))

\[ p < 0.05 \]
Effect of Osmolarity on PSC Proliferation and Activation

Osmolarity control had no influence on PSC proliferation after 48h incubation.
Immunostaining for α-SMA

Negative control

5.6 mM Glucose

33.6 mM Glucose

Osmolarity Control
Effect of Glucose Concentration on Type I Collagen Production in PSCs

Collagen Concentration in the Culture Medium (µg/ml)

Glucose (mM)

5.6  25.2  33.6

p < 0.05
High Glucose Concentrations:

1. Stimulate PSC proliferation
2. Activate PSCs
3. Stimulate collagen production in PSCs

Fibrosis and Sclerosis of the Pancreas
Diabetes Mellitus

Hyperglycemia \rightarrow Hypoinsulinemia

Activation of PSCs

Progression of Pancreatic Fibrosis

Acinar cell growth
Protein synthesis

Pressure Hypoxia

Chronic Pancreatitis

Endocrine Insufficiency

Alcoholic, Idiopathic
Thank you for your attention