Endocrine and Exocrine Functions of the Pancreas

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The pancreas is two in one: exocrine and endocrine gland. It is essential for digestion and the carbohydrate metabolism. Thus, a loss in pancreatic function leads to severe clinical symptoms. In this article, you will get a compact overview of the structure, functions, and diseases of the pancreas.

Macroscopic Anatomy of the Pancreas
Location of the pancreas

The pancreas is an elongated, tapered organ that is located across the back of the abdomen, right behind the stomach. It has a sigmoid shape and is organized in lobules, which are separated from each other by projections of the thin fibrous capsule that surrounds the organ, and by fine connective tissue septa.

Apart from the tail, the pancreas is a retroperitoneal organ that lies behind the peritoneal cavity, and is located deeply within the upper abdomen in the epigastrium and left hypochondrium regions. Some of its relations include the stomach superiorly and anteriorly, the colon and spleen laterally on the right and left respectively. The head of the pancreas is located on the right side of the abdomen and is connected to the duodenum through a small tube called the pancreatic duct.

The different parts can be distinguished as:

- **Caput pancreatis** (head of the pancreas): lies in the concave aspect of the duodenum (duodenal C) and has a hook-shaped process (uncinate process), which surrounds the superior mesenteric artery and vein.
- **Corpus pancreatis** (body of the pancreas): represents the main part of the pancreas and is contained within the posterior, retroperitoneal abdominal wall. The anterior part is covered with peritoneum and forms the posterior wall of the omental bursa.
- **Cauda pancreatis** (tail of the pancreas): stretches to the spleen and cannot be clearly differentiated from the body.
The microscopic anatomy involves 99% exocrine and 1% endocrine tissue by weight that is organized into acini that surround multiple ducts. The ducts eventually drain into the excretory duct which is the main pancreatic duct (or Wirsung’s duct). It runs across the whole gland and leads to the major duodenal papilla along with the common bile duct.

Due to the development of the pancreas out of two separate anlages (ventral and dorsal anlage), another accessory pancreatic duct (or Santorini’s duct) commonly exists, which leads to the minor duodenal papilla. The pancreatic duct runs along the length of the pancreas uniting with the common bile duct, forming what is called the hepatopancreatic ampulla of Vater. This structure opens into the duodenum.

Vascular supply of the pancreas

The coeliac trunk and the superior mesenteric artery ensure the arterial blood supply of the pancreas. The arteries reach the organ from both the cranial and the caudal side of the pancreas and form anastomoses in the area of the pancreatic head. This construction is referred to as the pancreatic arcade. It includes:

- Posterior and anterior superior pancreaticoduodenal artery (from the gastroduodenal artery, which originates from the coeliac trunk)
- Inferior pancreaticoduodenal artery (out of the superior mesenteric artery)

Additionally, the splenic artery in the area of the body and the tail of the pancreas gives rise to pancreatic rami, the dorsal pancreatic artery, and the greater pancreatic artery, which forms an anastomosis with the inferior pancreatic artery at the lower margin of the pancreas.

The pancreas drains into the splenic vein and the superior mesenteric vein, which eventually form the portal vein. Due to the close relationship between the pancreatic head and these vessels, cancer of the pancreatic head may cause constriction of the portal vein resulting in portal hypertension and stasis with ascites.
The pancreas is located in the posterior abdominal wall in a retroperitoneal manner. Thus, it has close topographic relations with a lot of structures:

- **Stomach**: the omental bursa separates the two organs. It lies anteriorly and superiorly.

- **Small intestine and duodenum**: while the small intestine can reach the lower margin of the pancreas anteriorly and medially, the pancreatic head clings closely to the duodenum.

- **Left kidney**: the pancreatic tail runs over the kidney.

- **Spleen**: the tail of the pancreas ends at the hilum of the spleen. Spleen located posteriorly and laterally. It is connected by ligaments to the tail of the pancreas.

- **Common bile duct**: can be embedded in the pancreas. Cancer of the pancreatic head can block the common bile duct, which results in obstructive jaundice.

- **Superior mesenteric artery and vein**: the vessels run dorsally to the head of the pancreas and emerge on the front side at the pancreatic notch. This is where they are entwined by the uncinate process. Cancer of the pancreatic head can spread to these two vessels, which can lead to circulatory disorders of several organs.

- **Splenic artery and vein**: the splenic artery is located on the upper margin of the pancreas, while the splenic vein runs deeper and behind the gland.
Malformations of the pancreas

The pancreas develops as two out-pouchings from the embryonic foregut; the dorsal and ventral pancreatic buds. Both remain attached to the gut and as the duodenum rotates during development, it takes with it the dorsal anlage leading to fusion of both the dorsal and ventral anlage to form the adult pancreas. The dorsal anlage forms the head, neck body and tail of the pancreas while the ventral anlage forms the uncinate process of the pancreas.

Pancreas divisum

If the ventral and dorsal pancreatic anlages do not merge during pancreatic development, a pancreas divisum occurs, which is characterized by two separate glands. The merging of the two pancreatic ducts stops here so that they can flow separately into the duodenum: the major pancreatic duct at the major duodenal papilla and the minor pancreatic duct at the more cranial lying minor duodenal papilla. This is quite frequent abnormality, which mostly does not cause any symptoms. In some cases, this anomaly is associated with recurrent episodes of pancreatitis. However, its role as a predisposition for pancreatitis is controversial.

Annular pancreas

During the development of the pancreas, a part of the ventral anlage (the right bud) moves around the duodenum from a dorsal location, while the other part (the left bud) regresses. If this regression does not occur, the left bud rotates around the duodenum ventrally and fuses with the right bud, which results in an annular pancreas: the descending part of the duodenum is encircled by pancreatic tissue. This rare anomaly can cause duodenal atresia.

Accessory pancreatic lobe

The accessory pancreatic lobe is a rare condition that presents with an additional pancreatic lobe arising from the main pancreatic gland with its own aberrant duct. The anomaly may present with recurrent pancreatitis.

Agenesis/hypoplasia of the pancreas

Total agenesis is incompatible with life and rarely occurs. However, hypoplasia/ lack of
development of one anlage may be seen. It may predispose one to diabetes mellitus especially if the dorsal anlage is involved, where islet cells are located.

Microscopic Anatomy of the Pancreas

In contrast to the macroscopic anatomy, the pancreas’ organization in the exocrine and endocrine pancreas becomes apparent in histological sections.
Exocrine part of the pancreas

Histologically, the exocrine part of the pancreas shows the typical structure of serous gland and represents roughly 98 % of the organ’s tissue. The acini consist of strong basophilic cells, which contain numerous secretory granules. Acini is made of zymogenic cells that surround a central lumen and is arranged in lobules.

Each lobule contains its own ductule, and many ductules join together to make intralobular ducts, which then form interlobular ducts that drain into branches of the main pancreatic duct. They contain inactive precursors of digestive enzymes, which are activated outside of the pancreas (see below) in order to prevent the organ from digesting itself. The acini are followed by intercalated ducts, which connect the acini to the ductal system.

A special feature concerning the histology of the pancreas is centroacinar cells, which represent invaginations of the intercalated ducts into the acinar lumen. With their bright coloration, they form a contrast to the acini and are easily identified in a histological picture. The pancreas lacks striated ducts, which can e.g. be found in the parotid gland. The ductal system consists of intralobular ducts with cuboidal epithelium, which fuse to form interlobular ducts with columnar epithelium. Eventually, these ducts lead to the major or minor pancreatic duct.

Endocrine part of the pancreas

About 2 % of the pancreatic tissue has an endocrine function. It is represented by accumulations of cells (islets of Langerhans) within the exocrine tissue. With their weak eosinophilic coloration, they differ from the dark acini of the exocrine part. The islets can be found mainly in the tail of the pancreas.

With immunohistochemical special stains, four different cell populations, each producing a different hormones, can be distinguished within the islets of Langerhans: alpha cells (20 %, particularly in the periphery, glucagon production), beta cells (70 %, evenly spread, insulin production), delta cells (5 %, somatostatin production), and PP cells (5 %, pancreatic polypeptide production).

Function of the Pancreas

An essential pancreas function is the conversion of food into fuel for the body’s cells. The exocrine part mainly produces digestive enzymes and helps in digestion, while the endocrine part is responsible for the regulation of the carbohydrate metabolism (blood
sugar) with its insulin and glucagon production.

Exocrine function of the pancreas

The pancreas produces roughly 1.5 to 2 liters of digestive secretion, which is lead to the duodenum via the pancreatic duct. This secretion consists of bicarbonate, which makes the fluid alkaline (pH 8), and of several enzymes, that are essential for digestion. *Trypsinogen* and *chymotrypsinogen* are inactive protease precursors (zymogens), which are activated by enterokinase in the intestinal lumen. These enzymes are secreted by zymogenic cells. The active enzymes *trypsin* and *chymotrypsin* are endopeptidases (fission of the peptide bond within a protein). This prevents the pancreatic tissue from digesting itself. Trypsin is able to activate other inactive enzymes.

*Carboxypeptidases* are also zymogens which are exopeptidases (fission of the peptide bond at the end of a protein) in their active form. Active enzymes in the pancreatic digestive secretion are *pancreas lipase* and *phospholipase A₂*, which hydrolyze triglycerides and phospholipids, *pancreas amylase* for breaking bonds in polysaccharides, and *(desoxy)* ribonucleases for the degradation of nucleic acids.

The release of these enzymes are regulated by hormones of the intestinal wall: *secretin*, which encourages the release of the alkaline secretion for neutralization of the acidic stomach content, and *cholecystokinin*, which stimulates the production and secretion of the enzymes. Gallstones in the common bile duct can cause secretion backflow. This can lead to premature activation of the enzymes with pancreatic self-digestion, which is referred to as *acute pancreatitis* (see below).

Endocrine function of the pancreas

The pancreas is not only digestive but also an endocrine gland. As such, it produces two important hormones of the carbohydrate metabolism: *insulin* and *glucagon*, amongst others. The anabolic hormone insulin is produced in the beta cells and is basally released in an oscillating manner. The half-life period in the blood is only six to eight minutes. A high blood glucose value acts as the main stimulus for induced release. Insulin then promotes the translocation of the insulin-dependent glucose transporter GLUT 4 to the plasma membrane so that the target cells can now quickly ingest glucose which decreases the blood glucose value.

Insulin also promotes *glycolysis* and *glycogen synthesis*. Thus, the absorbed glucose is either transformed into energy or it is stored. The direct antagonist of insulin is *glucagon*, which is produced in the alpha cells of the pancreas. At low blood glucose levels, glucagon promotes *glycoegenolysis* and *gluconeogenesis*. It inhibits glycolysis and glycogen synthesis so that the blood glucose level rises.

Therefore, it is a catabolic hormone that has an antagonist-effect concerning insulin. *Somatostatin*, which is produced by the delta cells, inhibits the secretion of insulin, glucagon, pancreatic enzymes, and gastric acid. *Pancreatic polypeptide* is produced by PP cells and also has an inhibitory effect I: It inhibits the release of pancreatic enzymes and the gallbladder release of bile.
Diseases of the Pancreas

Acute pancreatitis

**Acute pancreatitis** is characterized by autodigestion of pancreatic tissue due to premature activation of zymogens. The most frequent causes for this clinical picture are **choledocholithiasis** and **alcohol abuse**. The patients suffer from severe pain in the upper abdomen, which can spread to the back in a **belt-like manner**. **Nausea** and **vomiting** can occur, sometimes accompanied by fever. Ileus and jaundice are also possible symptoms. A circulatory shock, acute kidney failure, sepsis, respiratory arrest, heart failure, bleedings in the gastrointestinal tract and coma are feared complications.

Up to 30 % of these patients develop a pseudocyst that can regress spontaneously (see below). In the physical examination of a patient with acute pancreatitis, **abdominal tenderness** (elastic abdominal wall tension), **reddening of the face**, and sometimes bruising around the umbilicus (**Cullen’s sign**) and in the flank area (**Grey Turner’s sign**) stand out. **An increase in amylase and lipase** (> 3 times the normal value) in the serum can be found in the laboratory parameters, whereas lipase is specific to the pancreas.
An increase in GGT, AP, GOT, and bilirubin points to an obstruction of the common bile duct as a cause for pancreatitis.

**Treatment**

- Keep the patient nil per oral to rest the gland and avoid secretion and reactivating the digestive function.
- Supportive therapy with fluids and electrolytes avoids dehydration and electrolyte imbalances in a patient who is nil per oral with diarrhea and vomiting.
- Gallstones have to be removed. If conservative therapy fails, surgery should be the next step.

**Chronic pancreatitis**
The most common cause (80%) for **chronic pancreatitis** is **alcohol abuse**. In 10% of the cases, no cause for the disease can be identified (idiopathic). In contrast to acute pancreatitis, gallstones are not considered to be a cause for chronic pancreatitis. The main symptom is **recurrent pain** in the upper abdomen, which often lasts hours to days and is present in 90% of the patients. In many cases, this leads to further **abuse of alcohol** and **analgesics**.

The patients may also have diarrhea and weight loss due to poor feeding and increased losses via diarrheal stools. Only in later stages of the disease can the pain disappear completely. Due to the constant inflammation, a decline in pancreatic tissue occurs, which results in an exocrine and endocrine insufficiency.

This leads to **maldigestion** and **intolerance of certain kinds of food** (mainly fats) with nausea, vomiting, meteorism, weight loss, and **diabetes mellitus**. In earlier stages, these consequences can be reversible. In later stages with a ‘**burnt-out**’ gland, however, the pancreatic insufficiency is **irreversible**.

The determination of **elastase-1 in the stool** (< 100 micrograms/dL at insufficiency) can be performed as an indirect measuring of exocrine pancreatic insufficiency. **Calcifications** in the pancreas can be seen by sonography and are highly suggestive of chronic pancreatitis.

An abdominal CT scan is the gold standard method of investigation for chronic pancreatitis as calcifications are easily visualized as hyperdense lesions.

Causal therapy includes strict **alcohol abstinence** or the elimination of the underlying disease. In regards to the symptoms, the acute episode should be treated like acute pancreatitis. Therapy of the exocrine insufficiency consists of a **diet rich in carbohydrates** with many small meals and **substitution of pancreatic enzymes**.

Due to the endocrine insufficiency, patients become **insulin-dependent** (CAVE: risk of hypoglycemia). Since there is a risk for addiction to analgesics, they should be enrolled in a Pain Management Center. In most cases, the pain can be reduced by eliminating obstacles to drainage. This can be accomplished by ERCP with stent implantation because this decreases the pressure in front of the stenosis. **Pain that is resistant to therapy** presents an indication for **surgery**. The prognosis of chronic pancreatitis is poor, lethality amounts to 30-40% (within ten years).

**Pancreatic pseudocysts**
Pancreatic pseudocysts can present in the course of pancreatitis and disappear spontaneously in 50% of the cases. They consist of an accumulation of fluids, necrotic tissue, pancreas enzymes, and old blood. The main symptoms are a pain in the upper abdomen, nausea, vomiting, and weight loss. Further symptoms can occur due to compression of surrounding organs (intestinal tract, spleen, kidney).

However, pancreatic pseudocysts often are asymptomatic. Complications are a spontaneous rupture in the abdominal cavity and bleeding into the cyst. Sonography is suitable for diagnosis, in which the cysts present as anechoic structures with a hyperechoic rim. If there are cysts with a diameter of more than five centimeters spontaneous resolution over the ensuing months is less likely and cyst infection, a local complication, may occur. In these cases, surgery with cyst-jejunostomy or partial pancreatic resection may be necessary.

Diabetes mellitus

The physician encounters diabetes very often. Since insulin is the only hormone in the body that can decrease the blood sugar level, insulin deficiency results in an increase in glucose in the blood (hyperglycemia) and increased glucose excretion in the urine (glycosuria). There may be a relative or an absolute insulin deficiency.

With **type 1 diabetes**, there is an absolute insulin deficiency due to the destruction of the beta cells via autoantibodies. These patients are mostly young (between ages 15 and 25) and have to be substituted with exogenous insulin all their lives. Typical symptoms are increased thirst (polydipsia), increased urination (polyuria), weight loss, and reduced performance.

**Type 2 diabetes** is by far more frequent and characterized by resistance to insulin by peripheral cells so that a relative insulin deficiency occurs. It is also referred to as adult-onset diabetes since this disease mainly affects adults. In most patients, adiposis, hypertonia, and hypertriglyceridemia can be diagnosed. Along with diabetes mellitus, this quartet is referred to as the metabolic syndrome. In regards to therapy, a balanced diet, normalization in weight, and movement are important. **Oral diabetes drugs** are the medication of choice.
Mucoviscidosis

Mucoviscidosis or cystic fibrosis is a frequent metabolic disease that is inherited as an autosomal recessive trait. It is a multiorgan disease of exocrine gland function that mainly affects the lungs and the pancreas leading to chronic respiratory tract infections and pancreatic enzyme insufficiency.

It mainly affects the lungs and the pancreas. A mutation in the CFTR-gene leads to defective chloride channels in the ducts of exocrine glands which makes them produce a very viscous secretion that can obstruct the duct system of the gland. Thus, a cystic or fibrous conversion of the affected organ takes place, which gradually leads to loss of function.

Besides the lungs and the pancreas, the intestine, liver, bile ducts, and gonads can be affected so that the symptoms heavily depend on the affected organ. For the pancreas, the exocrine insufficiency is most important: Consequences are maldigestion with diarrhea and weight loss up to cachexia. Diabetes mellitus can possibly result due to the destruction of the islet tissue and, hence, a deficient insulin production. In the respiratory tract, they present with a persistent cough, wheezing, and restlessness.

The pilocarpine iontophoresis sweat test (measuring the chloride content in sweat. Pathological at values > 60 mmol/l) can be performed to ensure the correct diagnosis. Since mucoviscidosis is not curable, only symptomatic therapy can be carried out. Life expectancy is mainly limited by respiratory insufficiency and is roughly 40 years.

Note: An early diagnosis (if possible in the first half of the first year of life) is important in order to increase life expectancy.

Pancreatic carcinoma

Pancreatic carcinoma is the third most frequent tumor of the digestive tract, affecting men more frequently than women. The peak in disease onset is between the ages of 60 and 80. The causes are unknown, but smoking, adiposis, and heavy alcohol consumption are suspected to be risk factors. This adenocarcinoma originates from the epithelium of the duct and, in roughly 70 % of the cases, it is located in the head of the pancreas.
The absence of early symptoms makes pancreatic cancer hard to diagnose and this has a negative effect on the prognosis as it is recognized very late. Symptoms like upper abdominal pain, nausea, and weight loss make the differential diagnosis of chronic pancreatitis possible. Many patients report pain spreading to the back and jaundice, which points to a progressed stage of the disease.

Another symptom that is rather rare is a recurrent risk for thrombosis. If the body or the tail of the pancreas is affected, symptoms generally occur even later so that the prognosis is worse compared to cancer in the head of the pancreas.

Normally, the tumor is not palpable. However, the gall bladder is palpable if the tumor obstructs the common bile duct. Jaundice also results in this situation (Courvoisier’s sign). Tumor markers CA 19-9 and CEA should not serve for early diagnosis but are helpful in the post-surgery follow-up.

Only a few patients can be cured with the resection of the tumor since metastases are, in most cases, already there when the diagnosis is made. The results of chemo and radiation therapy are also not satisfactory. The latter is helpful,
however, in the therapy of the pancreatic pain. In most patients, **palliative interventions** (biliodigestive anastomosis, percutaneous stenting, and biliary drainage) are indicated. They can prolong life for six to nine months.

**Note:** pancreatic carcinoma = difficult diagnosis, difficult therapy, poor prognosis!

## Examination of the Pancreas

Due to its location in the retroperitoneal space, the pancreas is neither palpable nor can it be auscultated or imaged in a conventional x-ray. Pain expresses itself in the upper abdomen in a belt-like manner.

**Note:** the pancreas is not accessible for a simple physical examination! Often, a pancreatic disease is noticed when symptoms occur. With a carcinoma of the pancreatic head, jaundice can result due to an obstruction of the common bile duct (see above).

### Sonography

<table>
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<tr>
<th>The main structure for the localization of the pancreas is the splenic vein, which lies dorsally of it. The echogenicity is similar to the liver's; echogenicity increases with adiposis and increasing age (=pancreatic lipomatosis). Pancreatic tumors are normally hypoechoic. Calcifications are evidence of chronic pancreatitis. For better imaging of the tail of the pancreas, the ultrasound head should be rotated slightly clockwise.</th>
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### CT/MRT

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<th>In the sectional views, the pancreas lies in front of the vertebras in a hoof-shape.</th>
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### ERCP (endoscopic retrograde cholangiopancreatography)

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<th>Imaging of the bile ducts and pancreatic ducts with an application of contrast agents via the major duodenal papilla and screening afterward. If needed, a direct therapeutic intervention (papillotomy, stone extraction, drainage placement) is possible.</th>
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### MRCP (magnetic resonance cholangiopancreatography)

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<th>Non-invasive and does not involve radiation exposure. Imaging of fluids in the pancreatic ducts and the bile ducts as areas with high signal intensity, but no direct therapeutic intervention possible.</th>
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## Review Questions

The answers are below the references.

1. **Which statement concerning the topography of the pancreas is true?**

   A. The head of the pancreas reaches the hilum of the spleen.
   B. The pancreas is located primarily retroperitoneal.
   C. The splenic artery runs at the posterior surface and the splenic vein at the upper margin of the pancreas.
   D. The body of the pancreas forms the back wall of the omental bursa.
   E. The inferior mesenteric artery and vein transit from the posterior to the anterior surface of the pancreas at the pancreatic notch.

2. **Which histological structures cannot be found in the pancreas?**

   A. Intercalated ducts
   B. Acini
   C. Striated ducts
   D. Centroacinar cells
   E. Duct system

3. **Which statement concerning the function of the pancreas is true?**

   A. In the pancreas, the catabolic hormone insulin and the anabolic hormone glucagon are produced.
   B. Ribonucleases are produced as inactive precursors.
   C. With a pH of 6, the pancreatic secretion is alkaline.
D. The pancreas has both exocrine and endocrine functions.
E. The enzymes pancreatic lipase and phospholipase A2 are produced in the exocrine pancreas and participate in carbohydrate degradation.

4. Which statement concerning pancreatic carcinoma is false?
   A. Tumor marker C19-9 and CEA are suited for the diagnosis.
   B. Tumors in the body or the tail of the pancreas have the poorest prognosis.
   C. There are no early symptoms, which makes the diagnosis difficult.
   D. Jaundice can occur in tumors in the head of the pancreas.
   E. Courvoisier’s sign is characterized by a firm and elastic gall bladder and jaundice.

Patients frequently ask

Can you live without a pancreas?

Medically, it is possible to survive after the complete removal of the pancreas. However, in the absence of the pancreas, body is incapable to produce digestive enzymes, insulin, and other hormones to digest food and control blood sugar levels. Thus, the patient develops diabetes and he has to completely rely on exogenous insulin supply and other medicines to maintain sugar levels.

References


Correct answers: 1D, 2C, 3D, 4A

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