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REVIEW ARTICLE

Pancreas: Anatomy, Histology and Physiology

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ABSTRACT

Background: The pancreas is a multifunctional organ involving both endocrine and exocrine functions which plays a crucial role in metabolism and digestion. The pancreas extends horizontally from the C-loop of the duodenum to the splenic hilum, located retroperitoneally at the first and second lumbar vertebrae. The uncinate process, a small hook-like projection from the head of the pancreas, may be absent in about 10% of individuals. The pancreas produces both exocrine secretions (pancreatic juice from acinar cells) and endocrine hormones (insulin and glucagon). This review aims to provide a comprehensive overview of the morphological, physiological, and histological aspects of human pancreas development.

Conclusions: All professionals who treat problems of the human pancreas must possess thorough knowledge of its development, anatomy, histology, and physiology.

Keywords: Pancreas; Anatomy; Physiology; Histology.

INTRODUCTION

The pancreas functions as a heterocrine organ, exhibiting both endocrine and exocrine activities. Its anatomical structure includes distinct regions: the head, body, and tail, each contributing to its complex functionality. The exocrine pancreas is primarily responsible for producing digestive enzymes, such as amylase, lipase, and proteases, which facilitate the breakdown of carbohydrates, fats, and proteins in the small intestine. In contrast, the endocrine component, primarily composed of the islets of Langerhans, regulates blood glucose levels through the secretion of hormones like insulin and glucagon. The intricate histological organization of the pancreas, including the arrangement of acini and islet cells, is essential for understanding its physiological roles and the pathophysiology of various pancreatic disorders [1].

Recent advances in understanding pancreatic anatomy and physiology have shed light on several diseases associated with this organ. For example, type 1 and type 2 diabetes mellitus are linked to dysfunction in the islets of Langerhans, where autoimmune destruction of insulin-producing beta cells characterizes type 1 diabetes, while type 2 diabetes is associated with insulin resistance and impaired secretion. Chronic and acute pancreatitis are conditions resulting from inflammation of the pancreas, often due to alcohol abuse, gallstones, or genetic predispositions. These conditions highlight the importance of the pancreas's anatomical and histological integrity, as they can lead to structural changes, such as fibrosis and necrosis, impacting its function. Additionally, pancreatic cancer, particularly pancreatic ductal adenocarcinoma, is a malignancy closely related to the organ's histological architecture, with risk factors including chronic pancreatitis and genetic syndromes like familial pancreatic cancer [2].

Understanding the anatomy, physiology, and histology of the pancreas is crucial for diagnosing, treating, and managing these diseases effectively, as it allows clinicians to correlate structural changes with functional impairments, leading to more targeted therapeutic strategies. This review aims to elucidate these aspects of the pancreas, emphasizing their relevance in the context of current pancreatic diseases.

Embryology

The pancreas develops like other glands, starting with the formation of the duct, followed by cells growing around it to create gland lobules. The endocrine and exocrine tissues of the pancreas come

from the endodermal epithelium of the duodenum. During the second and third weeks of pregnancy, when the embryo is about 3.4 mm long, the pancreatic tissue begins to form from the duodenum as two buds, known as the ventral and dorsal buds [3].

The right and left ventral buds are distinct anatomical entities. The left ventral bud does not develop further and eventually regresses, whereas the right ventral bud, located between the duodenum and the common bile duct bud, continues to grow. Compared to the ventral buds, the dorsal bud is larger and positioned more superiorly. It grows toward the spine and is situated between the stomach and the dorsal mesentery of the duodenum. Ultimately, this development results in the formation of the superior part of the head, the entire body, and the pancreatic tail [4].

During development, the duodenum and stomach rotate in the embryo, shifting the ventral bud from the right to the left and posteriorly. The inferior part of the head and the pancreatic uncinate process are ultimately formed by the ventral bud, which ends up positioned behind and below the dorsal bud. Initially, each bud has its own separate duct. However, by the seventh week of gestation, both ducts fuse together. A section of the dorsal bud duct in the duodenal segment diminishes, while the remaining part joins with the ventral bud duct to form the pancreatic duct, which opens into the duodenum at the major duodenal papilla [5].

In pancreatic development, endocrine cells begin forming around the 7th to 8th week of gestation, with insulin-producing cells appearing first and dominating the first trimester. By the 8th week, glucagon- and somatostatin-producing cells emerge, followed by pancreatic polypeptide and ghrelin-expressing cells at the 9th week. Three main cell types form: insulin-only, glucagon-only, and dual hormone-producing cells, with dual cells peaking at 30% between 11 and 13 weeks, but dropping to less than 2% in adults. During weeks 9 to 16, glucagon-only cells increase while insulin-only cells decrease. By the 21st week, cell proportions resemble adult patterns. Somatostatin and pancreatic polypeptide are initially produced with insulin and glucagon, but by 15 weeks they separate, while ghrelin cells likely arise from a distinct lineage. Key transcription factors like sonic hedgehog (SHH), pancreatic and duodenal homeobox factor 1 (PDX1), GATA binding protein 4, GATA binding protein 6, and Sex determining region Y -box 9 (SOX9), appearing by weeks 4-5, are linked to permanent neonatal diabetes (PNDM) when mutated [6].

Disorders of pancreatic embryology can either remain asymptomatic or lead to obstructive pancreaticobiliary symptoms, such as recurrent or chronic pancreatitis, especially in childhood. One of the most common congenital malformations is pancreas divisum (PD), where the ducts of the ventral and dorsal pancreas fail to fuse, causing the dorsal pancreas to drain through the accessory duct of Santorini. While many individuals with PD are asymptomatic, those who do present clinically often experience recurrent or chronic pancreatitis. Anomalous pancreaticobiliary junction (APBJ) is a rarer ductal anomaly where pancreatic and bile ducts converge before entering the duodenum, resulting in reflux. Pancreaticobiliary reflux is more common due to pressure gradients favoring the entry of pancreatic enzymes into the bile, which can cause significant inflammation and increase the risk of biliary malignancies. [5].

Anatomy

The average volume of an adult human pancreas is approximately 72 cm^3, with dimensions ranging from 12 to 20 cm in length, 3 to 5 cm in height, and 1 to 3 cm in width. The pancreas has an elongated, hooked appearance and is divided macroscopically into the head, neck, body, and tail. It is located on the posterior wall of the abdominal cavity as a retroperitoneal organ. The duodenum surrounds the head of the pancreas, followed by the neck, which is situated near the superior mesenteric arteries. The body lies behind the posterior wall of the stomach, while the tail extends toward the hilum of the spleen [7].

Unlike the majority of human body glands, the pancreas lacks a well-defined fibrous capsule. The gland's tail is where the pancreatic duct begins and extends throughout the whole organ. On the major duodenal papilla, it joins the common bile duct to form the hepatopancreatic ampulla, also known as the Vater ampulla. 41–52.5% of people have an auxiliary pancreatic duct, also known as the duct of Santorini. In 30% of cases, it drains to the pancreatic duct and in the other direction, to the duodenum via the small duodenal papilla [5]. Anomalies of the pancreas, however, can lead to clinical conditions such as obstructive jaundice, pancreatitis, bilious emesis, and failure to thrive. Anatomical abnormalities can obstruct the bile or pancreatic ducts, leading to stasis, increased pressure, inflammation, and systemic complications like jaundice or pancreatitis [3].

Histology

The pancreas is a complex gland containing both endocrine and exocrine elements, based on its histology. The acinar cells are arranged around a central lumen in the exocrine part of the pancreas, which is classified as a complex tubuloacinar gland. These acini aggregate to form pancreatic lobules, which are separated by vascular connective tissue. The base of each pyramid-shaped acinar cell sits on the basal lamina, which separates them from the surrounding connective tissue. Each cell has a circular nucleus located at the base, surrounded by basophilic cytoplasm. The cell's apex, facing the acinar lumen, is rich in secretory granules containing proenzymes, known as zymogen granules [8].

The size of the Golgi apparatus, located between the zymogen granules and the nucleus, decreases as the concentration of zymogen granules increases. The basal cell membranes of acinar cells have receptors for the neurotransmitter acetylcholine and the hormone cholecystokinin (CCK). Electron micrographs of acinar cells reveal a high density of rough endoplasmic reticulum (RER) positioned at the base, along with numerous polysomes and many mitochondria containing matrix granules. Although the Golgi apparatus is well-developed, its size varies; it is larger after the zymogen granules release their contents and smaller when they are more abundant [9].

A pathway to the acinus lumen can be created by the fusion of multiple secretory vesicles or by the individual release of contents from the zymogen granules. The intercalated ducts connect the acini to the intralobular ducts, which drain into the interlobular ducts. The proximal section of this duct system is lined with simple squamous epithelium, while the distal section is lined with simple cuboidal epithelium. Mucous-secreting cells are present in the major ducts and larger interlobular ducts, which are surrounded by columnar epithelium [10].

The endocrine pancreas consists of islets of Langerhans, which are spherical, highly vascularized clusters containing approximately 3,000 cells each. The human pancreas contains one to two million islets, primarily located in the body and tail, where they form the pancreatic endocrine portion. Each islet, about 300 µm in diameter, is surrounded by reticular fibres that penetrate the islet and encircle the network of capillaries [11]. Each islet of Langerhans contains five distinct cell types: G cells, PP cells, delta (δ) cells (D and D1 cells), alpha (α) cells, and beta (β) cells. Routine histological examination cannot differentiate these cells, but immunocytochemical methods allow for their identification. The various cell types can also be distinguished by their granule size and electron density, visible in electron micrographs. The cells resemble those specialized in protein synthesis but lack any other specific morphological characteristics [12].

Islet mass and distribution within the pancreas are critical factors influencing the metabolic outcomes following pancreatectomy, which leads to a substantial loss of islet cell mass. Patients undergoing a partial pancreatectomy exhibit approximately 50% reduced insulin secretion, with the specific region resected impacting metabolic consequences. Notably, excision of the pancreatic tail is associated with elevated fasting glucose and impaired glucose tolerance, while removal of the pancreatic head may enhance oral glucose tolerance. Evidence suggests that islets in the head and tail of the pancreas exhibit functional heterogeneity, potentially linked to their distinct developmental origins. The head derives from both the dorsal and ventral pancreatic buds, whereas the body and tail originate solely from the ventral bud. Previous studies in rodent models have demonstrated that islets from the dorsal bud have a superior capacity for insulin secretion and synthesis compared to those from the ventral bud. This developmental programming may influence the functional characteristics of islets in adult life, thereby affecting strategies aimed at increasing functional β-cell mass in vivo. Understanding these differences is essential for optimizing therapeutic interventions for diabetes [13].

Most of the mass of pancreatic endocrine cells consists of β-cells. In pancreatic islets, the relative mass of β-cells ranges from 50 to 80 percent. Compared to alpha cells, β-cells have a spherical to ellipsoidal shape and show fewer aggregations of secretory granules. Adjacent β-cells have smooth plasma membranes with a narrow space between them. Cytoplasmic secretory granules store insulin, which is released by β-cells. These granules have a distinct structure, featuring a clear peripheral layer and an electron-dense core. A single β-cell contains approximately 9,000 to 13,000 secretory granules. The nucleus size, overall cell size, and granulation of β-cells in the human pancreas can vary significantly [14].

The size, shape, and nuclear outline of the α-cells are similar to those of the β-cells. With a smaller fraction than β-cells, they are grouped into tiny

groups of cells with detached ribosomes, mitochondria, and the Golgi apparatus confined. Glucagon is secreted by α-cells and is stored in secretory granules that have a characteristic shape, consisting of a greyish outer halo and an electron-dense center. An estimated 15-20% of the mass of islet cells are thought to be made up of α-cells. There can be large variations in the proportional volume occupied by α-cells among islets, with some having as much as 65% of α-cells [15].

Somatostatin-secreting D (or δ) cells account for 5–10% of the volume of the islets. Although all islet cells share characteristics with neurons, D-cells are most similar to small neurons. They often develop long, thin extensions resembling knob-like secretory granules. These processes often end near capillaries, suggesting targeted and potentially paracrine secretion. The PP cell, which secretes pancreatic polypeptide (PP), is the islet hormone that has received the least research attention. Immunocytochemical studies have identified this peptide hormone in two cell types: PP-immunoreactive cells with angular to round secretory granules, and another type with small granules previously referred to as D1 cells. The Ghrelin or epsilon cell is the newest identified cell type, comprising less than 1% of adult islets [16].

Pancreatic histology plays a crucial role in correlating tissue changes with clinical manifestations across various pancreatic diseases. In chronic pancreatitis, histological findings such as acinar atrophy, fibrosis, and ductal dilation correlate with clinical symptoms of chronic abdominal pain, malabsorption, and diabetes. Acute pancreatitis shows acinar cell necrosis, fat necrosis, and inflammation, which clinically manifest as sudden-onset severe abdominal pain and elevated pancreatic enzymes. In diabetes, type 1 is characterized by autoimmune beta-cell destruction in the islets of Langerhans, leading to insulin deficiency and hyperglycemia, while type 2 diabetes involves amyloid deposition and islet dysfunction, correlating with insulin resistance and metabolic syndrome [17].

Cystic lesions of the pancreas, such as serous cystadenomas, mucinous cystic neoplasms, and intraductal papillary mucinous neoplasms (IPMNs), show distinctive histological features like epithelial lining and stroma, with varying risks of malignancy. Clinically, they may present with nonspecific symptoms or be detected incidentally [18].

Physiology

From a physiological perspective, a variety of enzymes, including proenzymes trypsinogen, chymotrypsinogen, as well as pancreatic amylase, lipase, cholesterol esterase, ribonuclease (RNase), deoxyribonuclease (DNase), and elastase, are synthesized, stored, and released by the acinar cells of the exocrine pancreas using a bicarbonate-rich buffer solution. According to Berthelsen et al. [19], pancreatic amylase and lipase convert fats and carbohydrates into fatty acids and monoglycerides, respectively, and break down glycogen and carbohydrates into disaccharides. Moreover, cholesterol esters are broken down by pancreatic cholesterol esterase into cholesterol and fatty acids. Separating DNA from RNA is done by DNase and RNase, respectively. Elastase degrades elastin, which is the main building block of elastic fibres. [20].

Pancreatic secretion in response to a meal occurs in four distinct phases: cephalic, gastric, intestinal, and absorbed nutrient phases, each involving complex neural and hormonal regulation. The cephalic phase is triggered by sensory stimuli such as sight, smell, taste, and thought of food, which prepares the digestive system. The vagus nerve releases acetylcholine, stimulating pancreatic acinar cells to secrete digestive enzymes like amylase, lipase, and proteases even before food intake, accounting for 20-30% of total pancreatic secretion. The gastric phase occurs as food enters the stomach, where gastric distension and gastric juices stimulate neural reflexes via stretch receptors. The vagus nerve and gastrin enhance pancreatic secretion, contributing an additional 10-20%. The intestinal phase begins when chyme enters the duodenum and is responsible for the majority of pancreatic secretion (50-80%). Cholecystokinin (CCK), released in response to fatty acids and amino acids, stimulates acinar cells for enzyme secretion, while secretin, released due to acidic chyme, prompts bicarbonate secretion from ductal cells to neutralize gastric acid. Following nutrient absorption, the body regulates pancreatic activity based on the nutrient load, with fats stimulating bile release from the gallbladder to aid in fat digestion [21].

The regulation of pancreatic secretion is tightly controlled through feedback mechanisms. Proteolytic feedback occurs as amino acids and peptides stimulate CCK release during protein digestion. Intestinal hormones produced by enteroendocrine cells modulate both gastric and pancreatic secretion based on nutrient composition,

while bicarbonate secretion is crucial for neutralizing gastric acid and providing an optimal pH for enzyme activity. Disruptions in these regulatory mechanisms can lead to various gastrointestinal conditions, including exocrine pancreatic insufficiency, characterized by inadequate enzyme secretion and malabsorption, chronic pancreatitis that impairs secretory function, pancreatic cancer that alters secretion patterns, and malabsorption syndromes resulting from insufficient enzyme activity [21].

The islets of Langerhans cells of the endocrine pancreas are responsible for the production of insulin, ghrelin, amylin, glucagon, somatostatin, gastrin, and pancreatic polypeptide. Insulin and glucagon, two hormones that regulate blood glucose, are the most commonly produced hormones. The islets of Langerhans' β cells are where insulin is first produced. Any rise in blood glucose causes the release of insulin. The released insulin lowers blood glucose levels by binding to insulin receptors on the cell surface of many different types of cells, including skeletal muscle, liver, and adipose cells. Elevated blood levels of glucose, free fatty acids, amino acids, cortisol, growth hormone, stomach inhibitory peptide, secretin, CCK, and gastrin can all trigger the release of insulin [10].

In β-cells, low-affinity glucose transporters (GLUT1 and GLUT2) and glucokinase regulate glucose metabolism. In type 2 diabetes, this process is disrupted, affecting gene expression. Insulin secretion involves ATP production, closure of KATP channels, membrane depolarization, and calcium influx. Post-pancreatectomy studies suggest that β-cell function can improve independently of cell mass, and hyper-functional islets in obese individuals show elevated insulin secretion. Potential regenerative strategies include α-cell trans differentiation and stem cell-derived β-like cells, though β-cell heterogeneity within islets complicates restoration. Diabetes is viewed as a bihormonal disease, necessitating a broader focus on α-, β-, and δ-cells for full pathophysiological understanding [14].

Alpha cells produce glucagon, which acts primarily on hepatocytes, activating lipases and glycogenolytic enzymes, leading to hepatic gluconeogenesis and increased blood glucose. Despite glucagon's key role in counter-regulating insulin, α-cells are less studied than β-cells. The bihormonal hypothesis suggests that both hypoinsulinemia and hyperglucagonemia contribute to hyperglycaemia in type 2 diabetes (T2D), with T2D marked by excessive glucagon secretion and impaired suppression by glucose. Glucagon secretion is controlled by intrinsic α-cell mechanisms, extrinsic factors (e.g., GLP-1, GIP, somatostatin), and neural inputs. T2D alters these responses, affecting islet structure and function. Emerging research shows that GABA may transdifferentiate α-cells into β-like cells, while maintaining α-cell pools, indicating that both β-cell generation and α-cell preservation are important for glucose regulation. [13].

Somatostatin hormone decreases the motility of the gallbladder and digestive system and suppresses the release of hormones by α and β cells. Additionally, it suppresses the synthesis of hydrochloric acid (HCl) in the stomach and the release of pancreatic enzymes. Hyperglycaemia is brought on by the vasoactive intestinal peptide (VIP) and glycogenolysis. It controls the tone of the smooth muscles lining the digestive tract as well as intestinal motility. Additionally, intestinal epithelial cells' production of water and ions is regulated by VIP [22].

Another hormone released by G-cells is called glutathione. In addition to promoting the release of hydrochloric acid from the stomach and promoting motility and emptying, it also speeds up the pace at which gastric regeneration cells divide. The pancreatic polypeptide, released by PP-cells, increases the release of enzymes by the gastric main cells but inhibits the release of pancreatic enzymes, gastric HCL, and bile from the gallbladder. The hormone ghrelin, which is released from Ɛ-cells, stimulates hunger and controls the gastrointestinal tract's smooth muscle fibres' relaxation. And last, the hormone amylin, which is released by β-cells along with insulin. It mostly prevents emptying of the stomach. According to some research, amylin may also prevent glucagon from being released [23]. Dysfunction of islet cells can lead to pancreatic neuroendocrine tumours (PNETs), which represent about 7% of pancreatic masses. These tumours are typically slow-growing and well-differentiated, with 50-75% classified as non-functioning and not associated with hormone-related syndromes. [12].

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Consent for publication

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Competing interests

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