Anatomy and Physiology of the Pancreas

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Abstract

Mastery of the anatomy and physiology of the pancreas is fundamental in understanding the concepts involved in Pancreas transplantation. Normal anatomy and physiology are critical to appreciating the pathology of any organ system. The indications for transplantation require knowledge of both the normal and pathological states of the involved organ. A firm grasp of the blood supply, drainage, surrounding visceral anatomy, as well as the anatomical considerations of endocrine and exocrine pancreatic physiology are essential to graft function and survival. While this chapter's main focus is anatomy and physiology, the transplantation of the pancreas requires a multidisciplinary approach. As such, there are a number of topics that crossover with other chapters of this text. We will highlight those specific subjects and how they pertain to

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the core of this section. Upon completion of this chapter, the reader should feel comfortable with pancreas anatomy and physiology and how these concepts will impact pancreatic transplantation.

Keywords
Endocrine pancreas · Exocrine pancreas · Diabetes · Islet cells · Proteases

Introduction

The pancreas is an intricate organ with diverse function and the complexities of the pancreas have been studied substantially. The diverse array of anatomy and physiology of the pancreas merits their own individual chapters, within their own textbooks. It is imperative to understand the essentials of pancreatic anatomy and physiology in order to contemplate pancreatic pathology and the circumstances that lead to transplantation. This chapter will explain the anatomy and physiology of the pancreas on a gross and histological level. We will describe the pancreatic blood supply, venous drainage, and the organ's anatomical relationships and how they interplay with normal pancreatic function. Awareness of the embryological development of the pancreas aids in conceptualizing anatomical relationships and potential pathology. The endocrine and exocrine functions of the pancreas will be discussed in detail. These features play a role in pancreas pathology leading to transplantation as well as the surgical anatomy involved with the procedure itself. This chapter is but a small piece of the numerous concepts required for effective comprehension of contemporary pancreas transplantation.

Gross Anatomy

The pancreas is a retroperitoneal organ lying posterior to the stomach and anterior to the first lumbar vertebrae. It weighs roughly 100 g and is 14–20 cm in length (Hruban et al. 2007), about the size of half of a hand (Longnecker 2014). In Fig. 1, the organ and its surrounding anatomic relationships are displayed. The pancreas is divided into four anatomical parts: the head, neck, body, and tail. The head sits to the right of midline positioned within the C loop of the duodenum, anterior to the vena cava. The uncinate process, a projection off the inferior aspect of the head of the pancreas, extends behind the superior mesenteric vein (SMV) and anterior to the inferior vena cava sitting adjacent to the superior mesenteric artery (SMA) (Porrett 2010). The neck is a short segment that overlies the SMV and portal vein. The body and tail extend across the midline superior to the fourth portion of the duodenum forming the floor of the lesser sac. The tail extends into the hilum of the spleen. The intricate anatomic relationship between the pancreas and the main splanchnic blood vessels pose a challenge to the pancreatic surgeon. In the setting of pancreatic neoplasms, these vessels can be invaded, rendering surgery difficult at best or contraindicated at worst.

Embryology

During the fourth week of gestation, two endodermal tissues, the dorsal and ventral pancreatic buds, come together to form the pancreas. They are derived from pancreatic epithelial stem cells and give rise to the exocrine and endocrine cell lines. The dorsal bud is larger and forms the superior head, neck, body, and tail of the gland. The ventral bud develops as part of the hepatic diverticulum in communication with the biliary tree and migrates dorsally as the foregut and duodenum rotate in a clockwise fashion between the fourth and eighth week of development. Both develop from the primitive duodenal endoderm. Congenital abnormalities can lead to a variety of anatomical abnormalities and will be discussed later in this chapter. Normally, the ventral bud will form the uncinate process and the inferior portion of the head of the pancreas. The full development of acinar tissue extends into the postnatal period (Longnecker 2014).

The main duct, also known as the duct of Wirsung, is formed as the distal portion of the dorsal bud duct and ventral bud duct fuse in the

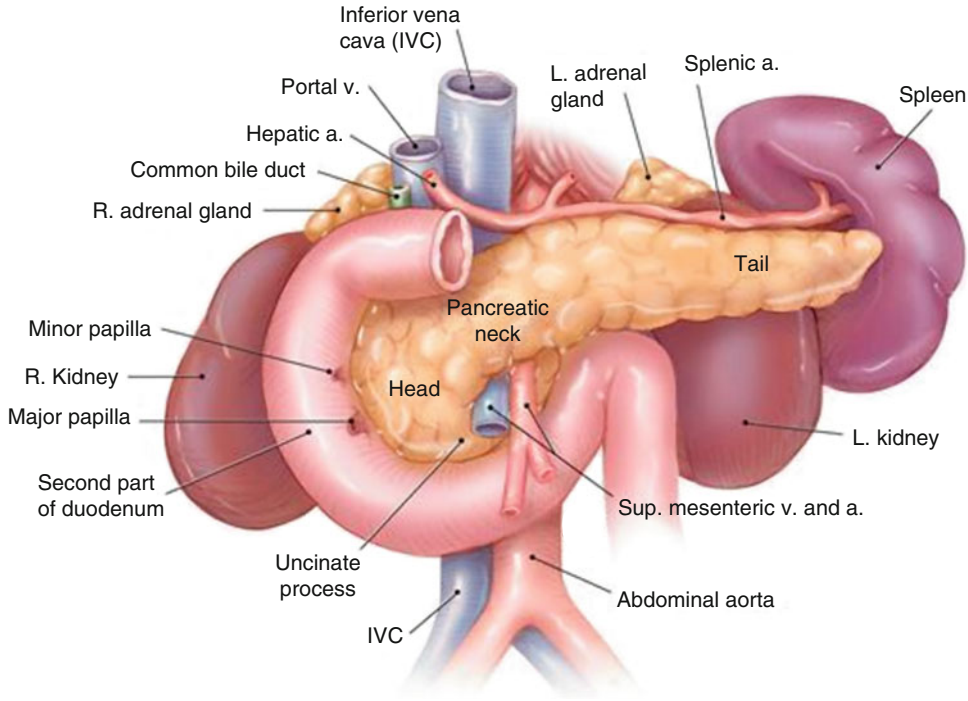

Fig. 1 Anatomic relationships of the pancreas with surrounding structures. (Image by Jennifer Parsons Brumbaugh used with permission of the publisher)

eighth week of gestation. The duct of Wirsung typically joins the common bile duct and enters the second portion of the duodenum at the major papilla. Anatomically, the aperture where biliary and enzymatic fluids enter the duodenum is known as the Ampulla of Vater and is surrounded by the Sphincter of Oddi. Just distal to this marks the embryologic transition between foregut and midgut. An accessory duct, the duct of Santorini, develops from the proximal portion of the dorsal bud duct. The accessory duct can be functional or nonfunctional. Also, it may directly communicate with the main pancreatic duct or may drain into the duodenum separately, via the minor papilla.

Abnormalities of fusion between the ventral and dorsal pancreatic ducts can result in pancreas divisum. Here, the dorsal duct drains the majority of pancreatic exocrine secretions into the duodenum via the minor duodenal papilla. The ventral pancreatic duct enters the duodenum via the major duodenal papilla, yet drains only the minority of pancreatic exocrine secretions (Sabiston and Townsend 2012). This abnormal drainage can lead to obstructed or refluxed pancreatic secretions, which frequently leads to a clinical presentation of pancreatitis.

On a microscopic level, the exocrine secretions are formed in the acinar tissues of the pancreas. The enzymatic effluent drains from an acinus into intralobular duct, which will course through pancreatic lobules. These ducts then lead to interlobular ducts which course between lobules. Eventually, the extensive network of intralobular and interlobular ducts drain into the main or accessory ducts (Longnecker 2014). The integrity of this ductal system is essential as leakage of enzymatic secretions can be damaging to surrounding tissue. Small perturbations in exocrine flow can lead to infiltration of effluent into the interstitial space of the pancreas. The local tissue damage manifests as pancreatitis, which can have varying phenotypic presentations from minor pain and inflammation to widespread pancreatic necrosis.

Other developmental anomalies in pancreatic gland formation exist. Annular pancreas is a result

of aberrant migration of the ventral pancreas bud. Here, pancreatic tissue can wrap circumferentially around the second portion of the duodenum (Sabiston and Townsend 2012). If tight enough, it can form a proximal gastrointestinal obstruction and require bypass with a duodenojejunostomy. Annular pancreas can exist on its own, or can be associated with other congenital defects including Down syndrome, malrotation, intestinal atresia, and cardiac malformations. Though not exactly anomalous, ectopic pancreatic tissue can arise anywhere along the primitive foregut. They are most frequently encountered in the stomach and duodenum. Along with gastric tissue, heterotopic pancreatic tissue may also be found in a Meckel's diverticulum (Sabiston and Townsend 2012). The caustic secretions from this tissue can cause ulceration of surrounding small bowel, becoming a more esoteric cause of gastrointestinal tract hemorrhage.

Initiation of pancreatic development is influenced by a number of molecular factors and pathways that influence its organogenesis. Of these, PDX1 (pancreatic duodenal homeobox 1), PTF1 (pancreas-specific transcription factor 1), notch-signaling pathway, critical to duct and acinar formation and exocrine differentiation, hedgehog signaling pathway, and Wnt signaling pathway have been found to be most critical. In PDX1 mouse knockouts, the pancreas never develops (Sabiston and Townsend 2012). 95% of acinar cells express PTF1, and in null mice, acini do not form. Though these proteins are key in pancreatic development, their exact roles and interactions are yet to be elucidated. It is the hope that these complex protein signaling pathways can one day be a target for pharmaceutical development.

Arterial Blood Supply

The arterial blood supply to the pancreas is a complex network of redundant vasculature cascading from the celiac trunk and SMA. Both of these blood vessels are solitary aortic branches displayed prominently in Figs. 2a, b. These arteries have branch extensively to provide splanchnic inflow and provide a rich collateral network around the pancreas (Longnecker 2014). Specifically, four named vessels provide the bulk of blood flow to the head of the pancreas. The anterior and posterior superior pancreaticoduodenal arteries arise from the gastroduodenal artery (GDA) and within the pancreas. They collateralize with the anterior and posterior inferior pancreaticoduodenal arteries, which arise from the SMA, prior to the first jejunal arterial branches. During pancreas procurement, it is important to preserve the vessels (Cameron and Cameron 2017). In the setting of small bowel procurement or liver with a replaced right hepatic artery, careful attention has to be given to the point of transection of the SMA. A pancreatic graft can still be procured for transplantation in these settings, but it is prudent to keep the inferior pancreaticoduodenal arteries in continuity with enough SMA to safely attach an iliac Y graft (to be discussed in later chapters). Likewise, a replaced right hepatic artery may arise from the SMA more proximally than the pancreaticoduodenal arteries. In this setting, the hepatic allograft can be isolated along with proximal SMA and a carrel patch of aorta while preserving the pancreas for transplantation. The neck, body, and tail receive arterial inflow from branches of the splenic artery and left gastroepiploic artery. The dorsal pancreatic artery, originating from the splenic artery, runs posterior to the body and becomes the inferior pancreatic artery supplying the body and tail. The greater pancreatic artery, of pancreatic magna, is the largest vessel supplying the pancreas from the splenic artery. It has a rare incidence of hemorrhage in the setting of pancreatitis, a complication which can be fatal. In general, the arterial supply is quite redundant, making the pancreas a richly vascular organ.

Venous Drainage

The venous drainage of the pancreas parallels the arterial system, although it drains into the portal system, rather than systemic circulation. The anterior and posterior inferior pancreaticoduodenal

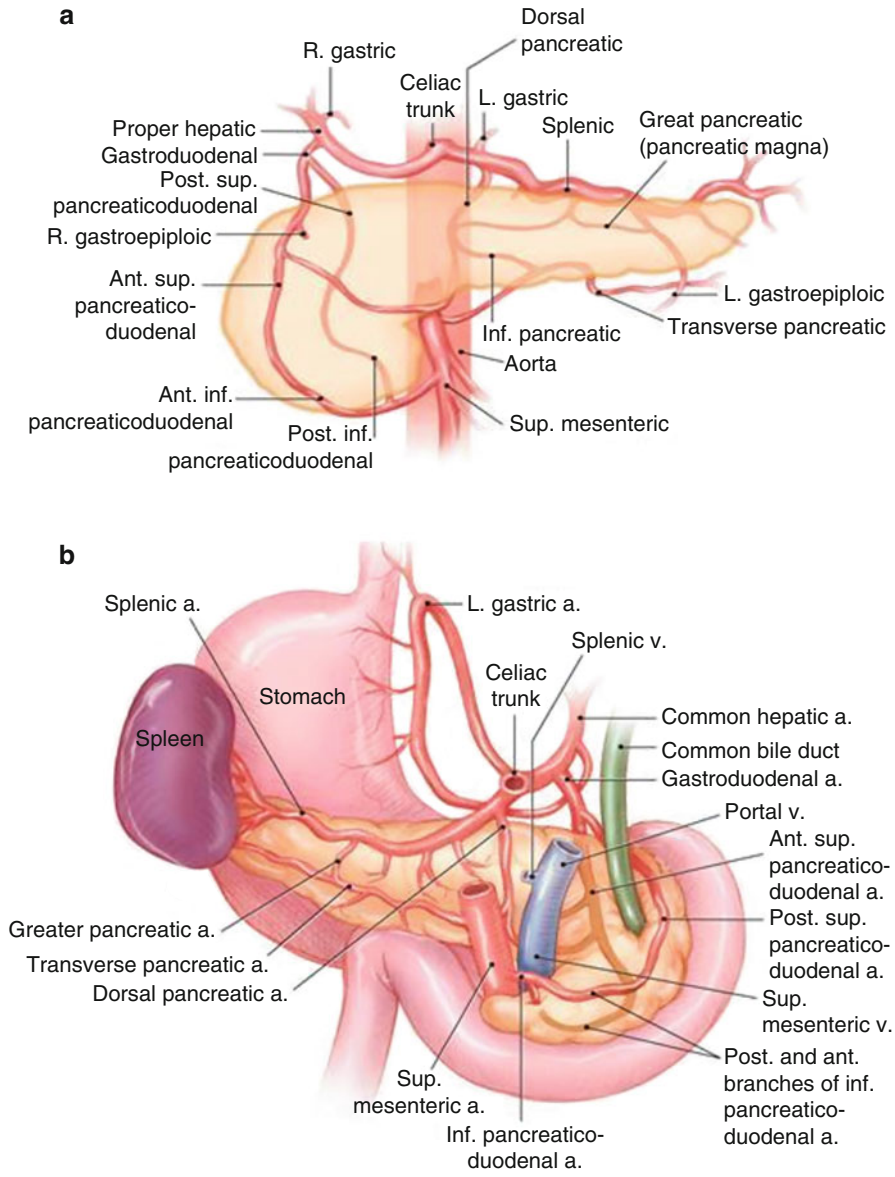

Fig. 2 Arterial blood supply of the pancreas from the front (**a**) and back (**b**). (Image by Jennifer Parsons Brumbaugh used with permission of the publisher)

veins drain the head of the gland. They then follow to the SMV at the superolateral border of the pancreatic neck. The anterior and posterior inferior pancreaticoduodenal veins drain most frequently into the right gastroepiploic vein prior to its confluence with the SMV at the inferior border of the pancreas. The venous drainage network can be somewhat variable, but eventually all venous drainage eventually enters the portal vein, formed posterior to the neck of the pancreas at the confluence of the splenic and superior mesenteric veins. During pancreas procurement, it is important to find a point on portal vein division that is amenable to the liver and pancreas transplant teams (the portal vein is an important source of hepatic allograft inflow and the only source of pancreatic

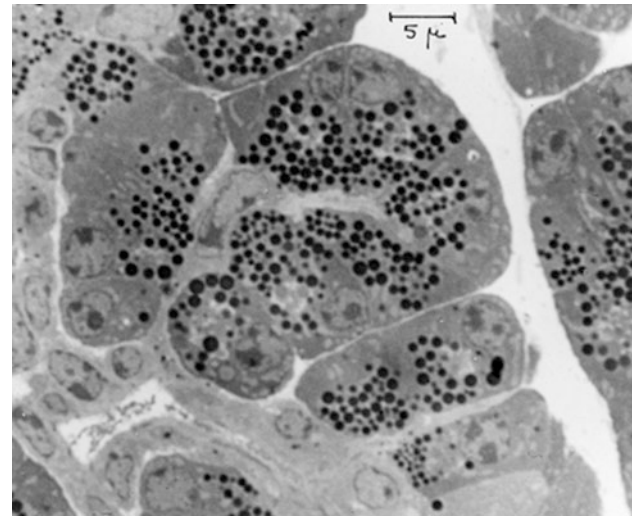

Fig. 3 Acinar and centroacinar cells under low power electron micrograph. (Attribution to Fred Gorelick; created by James Jamieson)

allograft outflow). There is individual variation in the location of the lymph nodes surrounding the pancreas although there are assigned lymph node station numbers that correspond to a relative anatomical location. However, these numbers are not often used in Western publications (Longnecker 2014).

Physiology

Exocrine Pancreas

The exocrine pancreas is a complex tubular network. It produces digestive enzymes (proteases) and bicarbonate-rich fluid providing the necessary components to aid in digestion. The acinar cells, which can be seen in Fig. 3, compose 85% of the pancreas and produce enzymes that digest proteins including trypsin, chymotrypsin, carboxypeptidase, and elastase. They are arranged in a complex intertwined tubular network (Longnecker 2014). Proteases are produced in inactive forms and stored as intracellular zymogen granules (Fig. 3). In the duodenum, enterokinase is produced which in turn activates trypsin from trypsinogen. Trypsin then further propagates proenzyme activation, leading to digestion. Pancreatic amylase and lipase are produced in their active forms hydrolyzing polysaccharides into oligosaccharides and fats into free fatty acids, respectively (Porrett 2010).

Ductal cells secrete bicarbonate-rich fluid under the influence of both vagal and humoral control. This provides the medium to deliver digestive enzymes to the gut and allows for the optimal basic pH for enzyme function. The content of pancreatic fluid can change based on the state of the pancreas. At low secretory rates, the concentrations of chloride and bicarbonate ions are similar to that found in normal plasma. With stimulation however, the concentration of bicarbonate increases dramatically while chloride decreases. In the current understanding of this mechanism, extracellular CO_2 diffuses across the basolateral side of the ductal cells. Inside the pancreatic duct cells, intracellular carbonic anhydrase hydrates the CO_2 to form HCO_3- and H+. Furthermore, an anion exchanger on the apical membrane of the pancreatic duct cells secretes intracellular HCO_3- into the pancreatic duct lumen for Cl−. The H+ byproduct is exchanged for a Na+ on the basolateral side of the pancreatic duct cell in order to maintain physiologic intracellular pH. Na+, K+ -ATPases provide the Na+ gradient that allows for HCO_3- secretion.

Pancreatic secretion occurs in different phases. In the cephalic phase, the pancreas is stimulated by vagal input in response to the sight, smell, or taste of food. This stimulation induces the

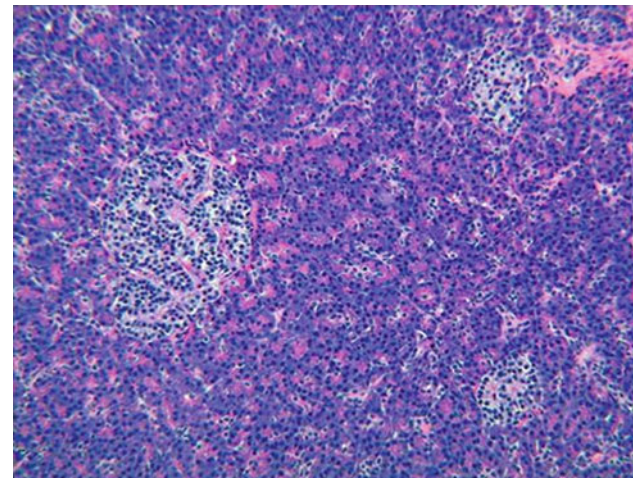

Fig. 4 Human pancreas with three islet cells. (Attribution to Dr. Daniel Longnecker MD)

secretion of pancreatic enzymes from acinar cells. In the gastric phase, vagal reflexes initiated by gastric distention yield additional acinar cell secretion of pancreatic enzymes. During the intestinal phase, acidification of the duodenal lumen causes the release of secretin from S cells. Once activated, secretin receptors cause an increase in cyclic adenosine monophosphate (cAMP) and activate the HCO_3-, Cl− exchanger, as well as increase the activity of carbonic anhydrase and excretion of H+. Lipids, proteins, and carbohydrates cause the secretion of cholecystokinin (CCK) once inside the duodenum, the main mediator of pancreatic enzyme secretion.

Endocrine Pancreas

In normal physiology, pancreatic exocrine function is extremely important. To the transplant surgeon however, pancreatic exocrine secretions need to be excreted. The surgical methods to eliminate pancreatic enzymes have long been the bane of pancreas transplantation. The endocrine pancreas is comprised of islet (islets of Langerhans) cells derived from the foregut endoderm and can be seen in Fig. 4. Islets can vary in size, the majority of which are between 50 um and 100 um in diameter (Hellman 1959). In humans, the number of islets is calculated to be between 500,000 and one million with the highest density in the tail of the pancreas. The acinar and islet cells differentiate from endodermal cells found in the embryonic buds. The main goal of the endocrine pancreas is to regulate the body's energy utilization, namely, carbohydrate metabolism.

Insulin is synthesized in the pancreatic beta cells comprising roughly 75–80% of the pancreas. Beta cell formation occurs before birth with additional proliferation through the second year of life. As plasma glucose levels increase, beta cell stimulation allows for proinsulin, the precursor for insulin, to synthesize and eventually cleave into insulin and residual C-peptide. Both are released directly into the bloodstream in equal amounts. In addition to glucose, a number of hormonal factors directly influence insulin release including gastric inhibitory peptide, glucagon, CCK, amino acids, and free fatty acids. Inhibitors of insulin secretion include somatostatin, amylin, leptin, and pancreastatin. Vagal and beta sympathetic stimulation augment insulin secretion, while alpha sympathetic stimulation inhibits insulin secretion.

Glucagon, secreted from alpha cells comprising 15% of the pancreas, functions to elevate blood glucose levels. Alpha cells appear in 3-week old embryos and organized islets appear at 10 weeks (Sabiston and Townsend 2012). Glucagon effectively stimulates glycogenolysis and gluconeogenesis in the liver. Glucagon is under tight hormonal and neural control and acts primarily in a reciprocal fashion to insulin in order to maintain glucose concentration in the blood.

Somatostatin, stimulated by acid in the duodenum, is secreted by delta cells comprising 5% of the cells of the pancreas and has profound inhibitory effects on the gastrointestinal tract. Somatostatin has been shown to inhibit the release of insulin, glucagon, and pancreatic polypeptide in addition to overall gastric, pancreatic, and biliary secretion. Synthetic versions of somatostatin are routinely used to treat many endocrine and exocrine disorders of the pancreas and gastrointestinal tract. Pancreatic polypeptide is secreted by F-cells under vagal control are considered the fourth most prevalent endocrine cell type. Most are derived from the ventral embryologic structures, ultimately the uncinate process. It decreases gallbladder and pancreatic secretion. Other peptides including VIP, amylin, galanin, and serotonin are secreted by pancreatic islets and have diverse roles. Other influencers on glucose homeostasis include an array of enteric peptide hormones released from the proximal gastrointestinal tract.

Anatomy of the Transplanted Pancreas

Significant effort is placed into the back table preparation of the transplanted pancreas. Proper arterial inflow and outflow are vital to graft viability, as the most common reason for early graft loss is thrombosis. As discussed earlier, the pancreatic allograft receives a dual blood supply from splenic artery, primarily supplying the body and tail of the gland, and superior mesenteric artery, primarily supplying the head and neck. There is extensive intrapancreatic vascular collateralization, allowing redundancy of arterial blood supply. A donor iliac Y-graft is used to reconstruct the superior mesenteric and splenic arteries, allowing a single recipient arterial anastomosis to be constructed at the time of implantation (Cameron and Cameron 2017). The specific surgical technique involved with pancreas transplantation will be discussed in this text.

Outflow of the pancreatic allograft is through the portal vein, which can be anastomosed to systemic circulation (iliac veins or vena cava) or splanchnic circulation (portal vein or SMV). Many transplant surgeons elect to use an iliac venous conduit to lengthen a foreshortened portal vein. Other surgeons are concerned the redundant portal vein may increase the thrombotic risk.

The duodenal C loop allows for proper excretion of pancreatic exocrine secretions. During the donor operation, the pylorus and segments 1–4 of the pancreatic graft are preserved. Remembering that the gastroduodenal artery is often sacrificed as part of the concurrent liver procurement, during the back table preparation of the graft, much of the duodenum is resected to eliminate sections that may have poor vascular supply. The final graft should contain a duodenal segment only large enough to contain the Ampulla of Vater and allow safe anastomosis formation. If used, a staple line along the duodenal conduit is often imbricated to reinforce this relatively ischemic segment of duodenum. Some surgeons elect to respect the entire duodenal segment entirely, performing instead a pancreatic ductal anastomosis. As will be discussed in a later chapter, there are many different strategies to allow for excretion of pancreatic enzymes.

Pancreas Transplant Physiology

Diabetes mellitus has its nomenclature rooted in Greek and Latin, literally meaning “sweet urine.” The disease represents a disorder of glucose metabolism, which leads to chronic hyperglycemia. Type 1 diabetes is the result of autoimmune or idiopathic beta cell destruction that ultimately leads to insulin deficiency. Evidence now suggests that this autoimmunity results from an imbalance between aggressive and regulatory T cell subsets (Orban et al. 2010). Type 2 diabetes is primarily a disease of insulin resistance and may be associated with varying degrees of beta cell dysfunction. Other less common causes of hypoinsulinemia include pancreatitis, trauma, or pancreatectomy.

Diabetes is a debilitating chronic disease, which leads to both macroangiopathies and microangiopathies. Macroangiopathic complications include coronary artery disease, cerebrovascular disease, and peripheral vascular

disease. Microangiopathic complications include retinopathy, peripheral neuropathy, and nephropathy leading to end-stage renal disease. Type 2 diabetics are typically initially treated with a prescription of lifestyle modification. Dietary changes along with an improved exercise regimen can improve insulin receptiveness alone. Many patients, however, will require oral medical therapy and some may need further insulin therapy to maintain euglycemia. Costs due to hospital admissions from diabetic complications are a significant burden to the healthcare system and the patient. Despite what a patient may perceive as euglycemia when they check glucose levels, daily fluctuations can still cause complications like blindness, renal failure, stroke, and heart attack. To avoid fluctuations, continuous glucose monitors may be more durable in second-to-second glucose monitoring. When properly treated, this may limit complications. Still though, life expectancy is significantly reduced and quality of life worsens as diabetes progresses.

Medical therapy of diabetes is constantly evolving and improving. The medical armamentarium to treat diabetes now includes rapid and long-acting insulin analogs, biguanides, gliptins, glitazones, and A-glucosidase inhibitors. An "artificial pancreas" system is currently available. Here, a continuous glucose monitors measures interstitial fluid glucose via a subcutaneous sensor and relays information to a monitor. This is then linked with an insulin pump, allowing a "closed loop" system to maintain tighter glycemic control without direct patient dosing.

For patients with difficult to manage type 1 diabetes who do not respond appropriately to conventional and conservative approaches to blood glucose management, whole pancreas transplantation is a treatment option. Allogenic islet transplantation is a less invasive approach; however, islet engraftment remains less durable than whole gland transplantation. Long-term insulin independence has remained inconsistent. As reported by the Collaborative Islet Transplant Registry, 70% of patients achieve insulin independence within their first year, but that number drops to 35% by year three.

While the ultimate goal of pancreas transplantation is independence from exogenous insulin therapy, in the face of advancing medical therapy, transplant rates have declined. Despite this, graft survival has improved to approximately 14 years (Lombardo et al. 2017). Today, pancreas transplantation is most commonly indicated in uremic Type 1 diabetic patients along with kidney transplantation. Less commonly, it is being performed either as a pancreas transplant alone or for Type 2 diabetes.

When successful, recipients of pancreatic allografts immediately return to normal fasting and postprandial glucose levels. Eventually, hemoglobin A1c levels return to normal levels. As reported by The International Pancreas Transplant Registry, 1-year graft survival rates have improved to 85% for SPK (simultaneous pancreas-kidney) transplants, 78% for pancreas after kidney transplants, and 76% for pancreas only transplants.

With decreases in morbidity and mortality, those patients who eventually become insulin independent report a better quality of life. In type 1 diabetics, for example, glucose-induced insulin secretion is restored thereby normalizing fasting glucose levels. Additionally, hypoglycemia-induced glucagon secretion and hepatic glucose production is restored as well (Barrou et al. 1994). Patients with long-standing autonomic neuropathy have been reported to have improved epinephrine response and normalization of hypoglycemia symptom recognition after pancreatic transplantation (Kendall et al. 1997). There is also a reported stabilization of their diabetic sequela. Retinopathy, nephropathy, neuropathy, and microvascular and macrovascular diseases associated with poor glucose control have been seen to improve after transplantation.

Conclusion

The value of pancreatic transplantation in the appropriate candidate cannot be understated. The anatomical and physiological concepts of the pancreas are paramount to understanding pancreatic pathology and successful transplantation. From this chapter and the others within this text, we

intend for the reader to have a well-balanced comprehension of the key concepts in contemporary pancreatic transplantation.

Cross-References

- Autologous Islet Cell Transplant
- Follow-Up Care of the Pancreas Transplant Recipient
- Medical Benefits of Pancreas Transplantation
- Medical Evaluation of the Diabetic Patient for Pancreas Transplant
- Surgical Complications of Pancreas Transplant
- Surgical Technique of Pancreas Transplantation
- UNOS Perspective on Pancreas Transplantation

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1. Gorelick and Jamieson (2005), Fig. 3.
2. Hruban et al. (2007), Figs. 1 and 2a, b.
3. Longnecker (2014), Fig. 4.

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