Presaditev trebušne slinavke: indikacija, kirurška tehnika, klinični pomen

Pancreas transplantation: indications, surgical technique, and clinical significance

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Izvleček

Presaditev trebušne slinavke je zlati standard za zdravljenje ledvične odpovedi pri bolnikih s sladkorno boleznijo oz. pri bolnikih s sladkorno boleznijo, kjer kljub intenzivirani inzulinski terapiji ne uspemo preprečiti nastanka kroničnih zapletov sladkorne bolezni. Z napredkom kirurgije in novimi imunosupresivnimi zdravili je v zadnjih desetletjih prišlo do bistvenega izboljšanja preživetja bolnikov in presadkov ter povečane kakovosti življenja po presaditvi. Presaditev trebušne slinavke je danes metoda izbire, s katero nadomestimo endokrino funkcijo trebušne slinavke, vzpostavimo normoglikemijo in preprečimo nastanek sekundarnih zapletov sladkorne bolezni. Med presaditve trebušne slinavke prištevamo sočasno presaditev trebušne slinavke in ledvice, presaditev samo trebušne slinavke, presaditev dela trebušne slinavke ter presaditev otočkov

Abstract

Pancreas transplantation (PT) is a vital therapeutic option for patients with diabetes mellitus (DM)|, particularly those with end-stage renal disease (ESRD) or severe metabolic complications. Over the past several decades, advancements in surgical techniques, organ preservation and procurement methods, and immunosuppression therapies have significantly enhanced post-transplant patient survival, graft survival, and quality of life. The primary goals of PT are to achieve effective and stable glycemic control, often leading to insulin independence, improve the patient's quality of life, and reduce secondary complications associated with DM. PT encompasses a variety of procedures, including PT alone from a living donor, whole PT, pancreas with kidney transplantation, and pancreatic islet cell transplanta-

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trebušne slinavke. Enoletno preživetje bolnikov po presaditvi trebušne slinavke znaša 96 %, petletno pa 80 %. Preživetje je najbolj optimalno pri sočasni presaditvi trebušne slinavke in ledvice.

tion. PT is most commonly performed in conjunction with kidney transplantation for selected patients with DM and ESRD. Over the past decade, unadjusted patient survival rates have exceeded 96% at 1-year post-transplant and > 80% at 5 years.

INTRODUCTION

Pancreas transplantation (PT) is a vital therapeutic option for patients with diabetes mellitus (DM), particularly those with end-stage renal disease (ESRD) or severe metabolic complications. Over the past several decades, advancements in surgical techniques, organ procurement and preservation methods, and immunosuppression therapies have significantly enhanced post-transplant patient survival, graft survival, and quality of life. The primary goals of PT are to achieve effective and stable glycemic control, often leading to insulin independence, improve the patient's quality of life, and reduce secondary complications associated with DM. (1-5)

PT encompasses a variety of procedures, including pancreas transplantation alone (PTA) from a living donor, whole PT, simultaneous pancreas-kidney (SPK) transplantation, and pancreatic islet cell transplantation (PICT). For select patients with DM and ESRD, SPK transplantation is most commonly performed. (3-6)

This review aims to provide a brief overview of the history, surgical techniques, and clinical outcomes of PT and PICT for patients with DM.

ANATOMY AND PHYSIOLOGY

The pancreas, which plays vital roles in digestion, absorption, utilization, and storage of energy substrates, is divided into two parts (exocrine and endocrine) that function together as an integrated glandular system despite having distinct structures. Both parts arise from the primitive gut. The exocrine pancreas is essential for nutrient digestion and is regulated by neural and hormonal signals, including gastrointestinal peptides, whereas the endocrine pancreas, which represents about 2% of the pancreas, is crucial for regulating glucose homeostasis. (2)

The endocrine portion consists of islets of Langerhans, which is composed of five cell types: β-cells (65%–80%) that produce insulin, α-cells (15%–20%) that release glucagon, δ-cells (3%–10%) that produce somatostatin, PP cells (1%) that contain pancreatic polypeptide, and ε-cells (less than 1%) that contain ghrelin. The exocrine pancreas, composed of acinar and ductal cells organized into a lobular branched structure, secretes digestive enzymes into the duodenum. (2)

Anatomically, the human pancreas is a solitary organ, measuring 14–18 cm in length, 2–9 cm in width, and 2–3 cm in thickness, with a weight of 50–100 g, and is divided into three main parts, including the head, body, and tail, although the boundaries are not sharply defined. The left border of the superior mesenteric artery (SMA) marks the boundary between the head and body, while the lengthwise midpoint defines the body–tail boundary. Some classifications identify a fourth and fifth part of the head: the uncinate process, located beneath the SMA, and the neck or isthmus, a thinner portion above the SMA. The head of the pancreas is C-shaped, aligning with the upper curvature of the duodenum. The body lies behind the stomach, extending almost horizontally across the abdominal aorta, inferior vena cava, portal vein, SMA, and superior mesenteric vein. The tail of the pancreas is located in the hilum of the spleen. (2)

Encapsulated by a fibrous capsule, the pancreas is divided by connective tissue septa into lobes and lobules. Mesenchymal tissue accounts for approximately 15%–25% of the total pancreatic volume and contains mainly fat cells. (2)

HISTORY OF PT

The history of PT spans several decades, marked by significant advancements that have evolved into a viable surgical option for patients with DM. The first successful PT was performed in 1966 at the University of Minnesota (Minneapolis, MN, USA). However, initial outcomes were poor due to challenges with surgical techniques, organ preservation, and immunosuppression. Nonetheless, persistent efforts and continued research has led to gradual improvements. By the 1980s, PT had gained more recognition, and with the advent of better immunosuppressive drugs, such as cyclosporine, patient and graft survival rates improved significantly. Today, PT is a well-established procedure that offers substantial benefits to select patients with DM. (1, 7, 8)

THE PT CANDIDATE

To our knowledge, there is no consensus statement specifying all indications for PT, although the typical candidate at most centers is a patient with type 1 DM and ESRD, coupled with adequate cardiac reserve. PTA is generally considered for DM patients with normal renal function—optimally, creatinine clearance > 70 ml/min—but who experience progressive complications, such as frequent, acute, severe metabolic issues (e.g., hypoglycemia, marked hyperglycemia, ketoacidosis), incapacitating clinical and emotional problems with exogenous insulin therapy, and consistent failure of insulin-based management to prevent acute complications. Due to rapid advances in insulin administration and glucose monitoring, defining "optimal" insulin therapy is challenging. PICT, a minimally invasive procedure involving the infusion of purified islet cells via the hepatic portal vein, is mostly performed for individuals contraindicated for PT or wish to avoid the associated risks. However, the long-term success rate (defined by insulin independence) of PICT is lower than PR and there have been no direct, randomized trials comparing the outcomes of these procedures. (9, 10)

CONTRAINDICATIONS FOR PT

Absolute contraindications, as adopted by most centers, include advanced cardiopulmonary disease, non-insulin-requiring DM, body mass index >35 kg/m², heavy smoking, severe peripheral vascular disease, moderate to severe dysfunction of other organ systems, active malignancy and infection, current substance addiction or abuse, and poor functional and performance status. (11)

There are also many relative contraindications that should be discussed with each patient before PT to ensure that the benefits outweigh the risks. (11)

SURGICAL PROCEDURE

Nearly 40 different technical approaches for PT have been described. The donor selection criteria for PT are more stringent as compared to other organs due to the high rate of graft rejection and low graft survival rate following transplantation. Typically, the pancreas is retrieved from a donor along with multiple intra-abdominal organs. After removal of the liver, the pancreas is resected *en bloc* along with the duodenum and spleen to ensure preservation of the vascular stumps of the SMA, splenic arteries, and portal vein. The pancreas must be rapidly dissected with minimal mobilization and without compromising the gland capsule. Afterward, the pancreatoduodenal graft is immersed in Belzer solution. (12, 13)

The pancreatoduodenal graft is prepared by removing the spleen, suturing, invagination of the duodenal borders, removal of excess fat surrounding the pancreas and ligation of small vessels and lymphatics along the inferior margin of the pancreatic tail, and mobilizing the portal vein. The SAM and splenic arteries are attached to a Y graft and the blood supply to the entire pancreas graft is assessed. At this stage, the graft is ready for implantation. (12, 13)

The pancreas allograft is typically placed intraperitoneally in the right iliac fossa of the recipient through a midline laparotomy, as the right iliac vessels are more accessible. There are two main options for venous drainage: portal or systemic via the vena cava, with the latter generally preferred due to ease

of implementation. While portal drainage is thought to offer potential metabolic benefits, this has not been definitively confirmed. Arterial anastomosis is usually performed with the common iliac artery of the recipient, provided it is not overly calcified. Exocrine drainage of the graft can be achieved through either side-to-side duodenojejunal anastomosis (enteric) or side-to-side duodenovesicular anastomosis (bladder). However, the use of bladder drainage has become less common due to a higher incidence of urinary complications. (12, 13)

Post-surgical follow-up typically involves monitoring in an intensive care unit. Recipients begin receiving immunosuppressive treatment during surgery, which includes antibody induction, and triple-drug immunosuppressive therapy is initiated immediately after the procedure. Heparin prophylaxis is also recommended, with intravenous heparin administered as a single dose during surgery after pancreas revascularization. Following surgery, either low-molecular-weight heparin or continuous infusion is continued to prevent thrombosis. (12-14)

COMPLICATIONS OF PT

PT is a complex surgical procedure that can lead to a range of postoperative complications impacting graft function and patient outcomes. These complications vary based on the type of transplantation—SPK, pancreas after kidney (PAK), or PTA—and the specific patient population. Postoperative complications can also be distinguished by the time of onset. (2, 12, 15)

Early complications, which are often related to technical factors, include:

- Vascular thrombosis: As the most common early complication, venous thrombosis is more frequent than arterial thrombosis, occurring in 7%–34% of patients, and often resolves with medical therapy. However, arterial thrombosis is more dangerous, leading to rapid graft loss. The appropriate use of anticoagulants, like heparin, can reduce this risk.
- Bleeding: A risk in approximately 5% of patients, often necessitating reoperation.
- Enteric anastomotic leakage: Leakage at the site of enteric anastomosis can lead to severe complications, including infection and sepsis.
- Graft pancreatitis: Can occur due to ischemia-reperfusion injury, leading to sepsis and exocrine leakage.
- Urologic complications: In transplants with bladder drainage, urologic complications can lead to metabolic complications, such as acidosis and dehydration. (12, 15)

Late complications include:

- Pseudocyst formation: Fluid collections that can become infected or cause pain.
- Pseudoaneurysms and arterio-venous fistulas: Can develop at vascular anastomosis sites.
- Loss of graft function. A significant complication of PT, occurring in approximately 10% of patients, with chronic rejection being the primary cause of long-term graft failure after 1 year.
- Other medical complications: Pneumonia, sepsis, and other infections due to immunosuppression. (16)

Effective post-PT monitoring involves a multidisciplinary team approach, including transplant surgeons, endocrinologists, nephrologists, radiologists, and other healthcare professionals working together to ensure the best possible outcomes for the transplant recipient. In SPK transplantation, both the pancreas and kidney are retrieved from the same donor, allowing changes in kidney function to serve as an indicator of potential rejection of either organ. This interconnected monitoring helps with early detection of rejection and ensures more coordinated management of both transplanted organs. (2)

CLINICAL SIGNIFICANCE

Patient survival rates after SPK, PAK, and PTA have significantly improved. Benefits can be assessed in terms of patient survival, stabilization, and improvement in DM complications and quality of life. (15, 17-18)

Over the past decade, unadjusted patient survival rates following PT have surpassed 96% at 1-year post-transplant and > 80% at 5 years. The leading causes of mortality after transplantation include cardiovascular and cerebrovascular events, as well as infections, which contribute to both early (<3 months) and late (>1 year) mortality. (15-17)

Graft survival has also improved, with unadjusted

1-year survival rates for SPK, PAK, and PTA of 89%, 86%, and 82%, respectively, and unadjusted 5-year survival rates of 71%, 65%, and 58%. The estimated half-life of pancreas grafts has increased to 14 years for SPK and 7 years for both PAK and PTA, with long-term survival of up to 26, 24, and 23 years, respectively. (15-18)

For type 1 DM patients, SPK transplantation can significantly extend lifespan as compared to kidney-only transplantation, with recipients achieving the highest longevity. Quality of life notably improves post-transplant, with patients reporting better physical, mental, and social functioning, higher energy levels, and optimism about the future. PT recipients, particularly after SPK, exhibit significant improvements in secondary complications of DM, such as nephropathy, neuropathy, gastroparesis, retinopathy, and cardiovascular issues. Successful PT effectively lowers glycated hemoglobin levels better than intensive insulin therapy, to maintain good glycemic control and improve lipid metabolism. (15-20)

Although PICT is less invasive, long-term outcomes are less favorable than PT. Nonetheless, PT provides higher rates of insulin independence and graft survival, as the preferred option for β-cell replacement therapy for insulin-dependent DM patients eligible for surgery. (1-6)

CONCLUSION

PT has evolved into a life-saving procedure, offering significant survival benefits and improved quality of life for patients with insulin-dependent DM. While the procedure carries challenges and risks, advancements in surgical techniques and immunosuppressive therapies have resulted in better outcomes for both patients and grafts over time.

REFERENCES

1. Gruessner RW, Gruessner AC. The current state of pancreas transplantation. Nat Rev Endocrinol. 2013 Sep;9(9):555-62.
2. Bahar SG, Devulapally P. Pancreas Transplantation. In: StatPearls. Treasure Island (FL): StatPearls Publishing; March 14, 2023.
3. Redfield RR, Rickels MR, Naji A, Odorico JS. Pancreas Transplantation in the Modern Era. Gastroenterol Clin North Am. 2016 Mar;45(1):145-66.
4. White SA, Shaw JA, Sutherland DE. Pancreas transplantation. Lancet. 2009 May 23;373(9677):1808-17.
5. Meirelles Júnior RF, Salvalaggio P, Pacheco-Silva A. Pancreas transplantation: review. Einstein (Sao Paulo). 2015 Apr-Jun;13(2):305-9
6. Wojtusciszyn A, Branchereau J, Esposito L, et al. Indications for islet or pancreatic transplantation: Statement of the TREPID working group on behalf of the Société francophone du diabète (SFD), Société francaise d'endocrinologie (SFE), Société francophone de transplantation (SFT) and Société française de néphrologie -dialyse- transplantation (SFNDT). Diabetes Metab. 2019;45(3):224-37.
7. Dean PG, Kukla A, Stegall MD, Kudva YC. Pancreas transplantation. BMJ. 2017;357:j1321. Published 2017 Apr 3.
8. Han DJ, Sutherland DE. Pancreas transplantation. Gut Liver. 2010;4(4):450-65.
9. Larsen JL. Pancreas transplantation: indications and consequences. Endocr Rev. 2004 Dec;25(6):919-46.
10. Gruessner RW, Gruessner AC. Pancreas transplant alone: a procedure coming of age. Diabetes Care. 2013 Aug;36(8):2440-7.
11. Shyr YM. Pancreas transplantation. J Chin Med Assoc. 2009;72(1):4-9.
12. Hampson FA, Freeman SJ, Ertner J, et al. Pancreatic transplantation: surgical technique, normal radiological appearances and complications. Insights Imaging. 2010;1(5-6):339-47.
13. Lam VW, Pleass HC, Hawthorne W, Allen RD. Evolution of pancreas transplant surgery. ANZ J Surg. 2010;80(6):411-8.
14. Boggi U, Vistoli F, Egidi FM, et al. Transplantation of the pancreas. Curr Diab Rep. 2012;12(5):568-79.
15. D'Alessandro C, Todisco M, Di Bella C, Crimì F, Furian L, Quaia E, Vernuccio F. Surgical complications after pancreatic transplantation: A computed tomography imaging pictorial review. World J Gastroenterol 2023; 29(46): 6049-59
16. Maupoey Ibáñez J, Boscà Robledo A, López-Andujar R. Late complications of pancreas transplant. World J Transplant. 2020;10(12):404-14.
17. García-Padilla P, Dávila-Rúales V, Hurtado DC, Vargas DC, Muñoz OM, Jurado MA. A Comparative Study on Graft and Overall Survival Rates Between Diabetic and Nondiabetic Kidney Transplant Patients Through Survival Analysis. Can J Kidney Health Dis. 2023;10:20543581231199011. Published 2023 Sep 14.
18. Lombardo C, Perrone VG, Amorese G, et al. Update on pancreatic transplantation on the management of diabetes. Minerva Med. 2017;108(5):405-18.
19. Boggi U, Vistoli F, Andres A, et al. First World Consensus Conference on pancreas transplantation: Part II - recommendations. Am J Transplant. 2021;21 Suppl 3(Suppl 3):17-59.