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Pancreas Transplant: Brief Review Of The Journey, Current Evidence And Future Prospects.

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Introduction:

Pancreas transplantation has emerged as a ground breaking medical intervention for individuals suffering from diabetes mellitus, offering a potential resolution to the root cause of the disease. This review seeks to explore the realm of pancreas transplantation in greater depth. It encompasses the historical progression, nuanced surgical methodologies, intricate immune suppression protocols, resultant clinical effects, and the encouraging trajectories that offer promise in propelling this field forward. This article also entails the current scenario of pancreas transplant in India as well as the latest upgradation in techniques and modalities of pancreas transplant.

History:

The origins of pancreas transplantation trace back to the 1960s, when a team of surgeons, led by Dr. Richard Lillehei, achieved a significant breakthrough by successfully executing the inaugural pancreas transplant in human patients.[1] This monumental accomplishment represented a pivotal stride towards tackling the fundamental underpinnings of type 1 diabetes, an autoimmune ailment characterized by the destruction of insulin-producing beta cells within the pancreas.[1]
Despite this initial triumph, the nascent endeavours encountered hurdles in sustaining graft function due to insufficiently robust immunosuppression measures and organ preservation techniques.[2] The subsequent decade, the 1970s, maintained a steadfast interest in pancreas transplantation as a prospective remedy for diabetes.[2] Surgeons and researchers embarked on exploring diverse methodologies pertaining to graft positioning, vascular anastomoses, and immunosuppression strategies.[2] Yet, outcomes persisted as less than optimal, marked by constrained graft viability and notable surgical risks.[2]
A turning juncture emerged in the narrative of pancreas transplantation with the advent of the simultaneous pancreas-kidney transplant (SPK).[3] Spearheaded by Dr. Paul Lacey and Dr. David Sutherland, this technique aimed not only to restore insulin production but also to address the kidney impairment often experienced by diabetes patients.[3] By combining a functional pancreas transplant with a kidney transplant from the same deceased donor, the SPK procedure triumphed in nullifying the necessity for dialysis, thus dramatically enhancing the recipients' quality of life.[3]
The 1990s ushered in a phase characterized by honing surgical methodologies, refining immunosuppressive protocols, and elevating criteria for patient selection.[4] Refinements in microsurgery yielded more precision in vascular anastomoses, while advancements in immunosuppressive agents mitigated episodes of rejection.[4]

The incorporation of bladder drainage techniques and the utilization of the enteric system for exocrine drainage further elevated graft functionality.[4] Concurrently, the domain of pancreas transplantation expanded to encompass pancreas-after-kidney transplants (PAK) for individuals who had previously undergone kidney transplantation.[4] Moreover, the concept of pancreas-alone transplants (PAT) gained traction as a treatment avenue for severe type 1 diabetes cases not necessitating kidney transplantation.[4]
In the contemporary landscape, pancreas transplantation continues its evolution through the integration of minimally invasive surgical modalities, individualized immunosuppressive regimens, and the exploration of avant-garde therapies like regenerative medicine and xenotransplantation. The latter involves utilizing organs from other species. Ongoing research diligently strives to enhance graft survival, ameliorate immunosuppression-related adverse effects, and expand the donor pool through initiatives such as living donor pancreas transplantation and the refinement of organ preservation techniques

Indications of Pancreas transplant:[3]
- Severe complications of diabetes mellitus with frequent and severe hypoglycemia or ketoacidosis.
- Poor quality of life in spite of insulin therapy.
- Patients with type 1 diabetes with end-stage renal failure on dialysis.

***Table 1**: Eligibility criteria for pancreatic transplant [3]*

Transplant type	Eligibility
Pancreas transplant alone	• Insulin-treated type 2 diabetes mellitus with body mass index ≤30 kg/m^2 or • Type I diabetes mellitus with at least two severe hypoglycaemic states within last 24 months and be specially assessed as having disabling hypoglycaemia
Simultaneous kidney pancreas transplant	• Pancreas transplant alone requirements and • Receiving dialysis or glomerular filtration rate <20 mL/min

Types of pancreas transplant:

Pancreas transplantation has evolved to encompass different types of procedures tailored to varying clinical scenarios. Each type serves a specific purpose, addressing the unique needs of individuals with diabetes and related complications. The primary types of pancreas transplant procedures are as follows:

- **Simultaneous Pancreas-Kidney Transplant (SPK):** The SPK procedure involves the transplantation of both a healthy pancreas and a kidney from a deceased donor into a recipient with type 1 diabetes and end-stage renal disease (kidney failure). This approach addresses both the underlying cause of diabetes and the kidney dysfunction caused by the disease. Successful SPK transplantation aims to restore normal glucose control, eliminate the need for insulin therapy, and provide a functioning kidney, alleviating the need for dialysis.[5]
- **Pancreas After Kidney Transplant (PAK):** In cases where a patient has previously received a kidney transplant due to diabetic kidney complications, a pancreas after kidney transplant (PAK) can be considered. This procedure involves transplanting a healthy pancreas into a recipient who already has a functioning kidney transplant. The goal of PAK transplantation is to improve glycemic control and prevent diabetes-related complications, without the need for dialysis.[6]
- **Pancreas Alone Transplant (PAT):** A pancreas alone transplant (PAT) is performed on individuals with severe type 1 diabetes who do not require a kidney transplant. PAT aims to provide euglycemia (normal blood sugar levels) and alleviate hypoglycemic unawareness by replacing the malfunctioning pancreas with a healthy one. This procedure offers the potential to significantly improve quality of life for those with difficult-to-control diabetes.[7]
- **Islet Cell Transplantation:** Islet cell transplantation is a minimally invasive procedure that involves isolating insulin-producing islet cells from a deceased donor's pancreas and then infusing them into the recipient's liver. This procedure is primarily considered for individuals with type 1 diabetes who experience severe hypoglycemic episodes and are not suitable candidates for whole pancreas transplantation. Islet cell transplantation aims to restore insulin production and reduce the risk of severe low blood sugar episodes.[8]
- **Living Donor Pancreas Transplant:** Living donor pancreas transplantation is an innovative approach where a healthy individual, often a family member, donates a portion of their pancreas to a recipient in need.

This procedure is less common than deceased donor transplantation due to the complexity and risks involved. It can be considered in specific cases where a suitable deceased donor pancreas is not available or when the recipient has a willing and compatible living donor.[9]

Table 2: *Pancreas transplant types: Advantages and Disadvantages[10]*

Transplant type	Advantages	Disadvantages
Simultaneous pancreas-kidney (SPK), 80%	One operation Simillar protocol in immunosuppressants Easier to detect pancreas rejection early by monitoring kidney graft Better outcome	More advanced diabetic complications
Pancreas-after-kidney (PAK), 15%	Already immunosuppressed	Two operations More advanced diabetic complications More difficult to detect pancreas rejection early Mediocre outcome
Pancreas transplantation alone (PTA), 5%	Lower surgical risks with less or no diabetic complications	Early exposure to immunosuppressants More difficult to detect pancreas rejection early Mediocre outcome

Surgical techniques [11]:

Pancreas transplantation involves a series of intricate surgical procedures that demand meticulous attention to detail. Surgeons perform vascular anastomoses to establish blood flow, while bladder/enteric drainage techniques are employed to facilitate the passage of pancreatic secretions. The advent of microsurgical techniques has minimized complications, and minimally invasive approaches have been explored to enhance patient recovery. Furthermore, the optimization of organ preservation methodologies has contributed to preserving graft integrity during transportation and transplantation. Surgical techniques in pancreas transplantation have evolved over the years to improve outcomes, reduce complications, and enhance patient recovery. Here are the key surgical aspects of pancreas transplantation:

- **Graft Placement**: The placement of the transplanted pancreas is a critical step in the surgical procedure. The pancreas can be placed either in the pelvis (retroperitoneal) or the right lower quadrant of the abdomen. The choice of placement depends on the surgeon's preference, recipient anatomy, and technical considerations.
- **Vascular Anastomoses**: Vascular anastomoses involve connecting the blood vessels of the transplanted pancreas to those of the recipient. This step ensures proper blood supply to the graft. Two major anastomoses are performed: the portal vein anastomosis, which connects the graft's portal vein to the recipient, and the arterial anastomosis, which connects the graft's artery to the recipient's iliac artery.
- **Exocrine Drainage:** The pancreas produces digestive enzymes that need to be drained properly after transplantation. There are two main approaches for exocrine drainage: enteric drainage and bladder drainage. Enteric drainage involves connecting the pancreas graft's duodenum to the recipient's small intestine, allowing digestive enzymes to flow into the intestinal tract. Bladder drainage involves connecting the pancreas graft's duodenum to the recipient's bladder, allowing drainage through urine.
- **Minimally Invasive Techniques:** In recent years, minimally invasive techniques have been explored to reduce surgical trauma and promote faster recovery. Laparoscopic-assisted pancreas transplantation involves making smaller incisions and using laparoscopic tools to perform parts of the procedure. However, the complexity of pancreas transplantation limits the extent to which this approach can be used.
- **Organ Preservation**: Proper organ preservation is crucial to maintain the viability of the donor pancreas between procurement and transplantation. Cold preservation techniques involve flushing the pancreas with a cold preservation solution and placing it on ice. Machine perfusion techniques involve using a specialized device to maintain oxygenated blood flow to the pancreas, enhancing preservation quality.

- **Living Donor Techniques**: In living donor pancreas transplantation, a portion of the healthy pancreas from a living donor is transplanted. This procedure involves intricate dissection and reattachment of blood vessels and ducts in both the donor and recipient. The goal is to ensure proper blood supply and drainage while maintaining optimal function in both individuals.
- **Combined Procedures:** Pancreas transplantation can be combined with kidney transplantation (SPK or PAK), necessitating coordination of surgical techniques for both organs. Additionally, pancreas transplantation can be combined with other surgical procedures, such as liver transplantation for certain cases.

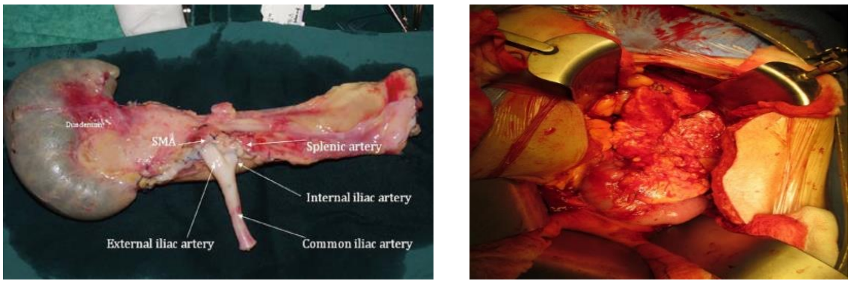

Figure 1 (a)*Explanted pancreas specimen after reconstruction (b)Implanted pancreas[10]*

Immunosuppressive Protocols [12]:

Immunosuppression regimens are a crucial component of pancreas transplantation to prevent the recipient's immune system from attacking and rejecting the transplanted pancreas. These regimens aim to strike a balance between suppressing the immune response and minimizing the risks of infections and other complications. The choice of immunosuppression regimen depends on factors such as the recipient's medical history, risk factors, and the type of pancreas transplant performed. Here are some common immunosuppression medications and regimens used in pancreas transplantation:

- **Induction Therapy**: Induction therapy involves administering potent immunosuppressive medications shortly after transplantation to provide intense immunosuppression during the critical initial period. Common induction agents include Antithymocyte Globulin (ATG) which is a polyclonal antibody that targets T cells and helps prevent acute rejection. Basiliximab and Daclizumab are monoclonal antibodies that specifically target interleukin-2 receptors on activated T cells.
- **Maintenance Immunosuppression**: Maintenance immunosuppression aims to provide ongoing immune suppression while minimizing adverse effects. A combination of medications is typically used, and regimens may vary based on individual patient needs. Common maintenance medications include Calcineurin Inhibitors (CNI) like Tacrolimus and Cyclosporine which inhibit the activation of T cells by blocking the calcineurin pathway and Antiproliferative Agents like Mycophenolate Mofetil (MMF) or Azathioprine which target rapidly dividing cells, including activated immune cells. Corticosteroids like Prednisone are also used which help in controlling inflammation and immune responses.
- **Personalized Regimens**: Immunosuppression regimens are often tailored to individual patients based on factors such as age, medical history, risk of rejection, and previous response to medications. The goal is to achieve the right balance between preventing rejection and minimizing side effects.
- **Conversion Therapy**: In some cases, patients may undergo conversion therapy, which involves changing or adjusting immunosuppression medications to optimize graft function or reduce side effects.
- **Monitoring and Adjustment**: Regular monitoring of immunosuppression levels, kidney function, and other relevant parameters is essential to ensure the right balance of immune suppression. Medication dosages may be adjusted based on these monitoring results.
- **Biologic Therapies:** Newer biologic therapies are being researched and developed to provide targeted immune suppression. These therapies aim to reduce the risk of rejection while minimizing the impact on overall immune function.

Clinical Outcomes:

Clinical outcomes in pancreas transplantation are a critical measure of the procedure's success and its impact on the health and well-being of transplant recipients. These outcomes provide valuable insights into the effectiveness of the transplantation process in achieving glycemic control, reducing diabetic complications, and enhancing overall quality of life. Here are some key clinical outcomes associated with pancreas transplantation:

- **Glycemic Control**: One of the primary objectives of pancreas transplantation is to restore normal blood glucose levels. Successful transplantation can lead to euglycemia (normal blood sugar levels) and reduce or eliminate the need for exogenous insulin therapy. Improved glycemic control reduces the risk of hyperglycemia-related complications such as cardiovascular disease, neuropathy, and retinopathy.[13]
- **Insulin Independence**: A significant clinical milestone is the achievement of insulin independence. Transplant recipients who no longer require insulin injections experience improved daily life, reduced financial burden, and enhanced freedom from the constraints of diabetes management.[13]
- **Diabetic Complications**: Pancreas transplantation has shown the potential to mitigate or halt the progression of diabetic complications. These complications include nephropathy (kidney damage), neuropathy (nerve damage), retinopathy (eye damage), and cardiovascular diseases. Improved blood sugar control after transplantation can lead to a reduction in the severity of these complications.[13]
- **Quality of Life**: Perhaps one of the most impactful outcomes of pancreas transplantation is the enhancement of recipients' overall quality of life. Freedom from insulin injections, stable blood sugar levels, and reduced risk of hypoglycemic episodes contribute to improved physical, emotional, and psychological well-being.[14]
- **Hypoglycemic Unawareness:** Severe hypoglycemic unawareness, a condition in which individuals with diabetes are unable to sense low blood sugar levels, can be life-threatening. Successful pancreas transplantation often alleviates this condition, reducing the risk of dangerous hypoglycemic episodes.[14]
- **Kidney Function Improvement**: For patients undergoing simultaneous pancreas-kidney transplantation (SPK), the kidney transplant provides added benefits. Improved kidney function and the prevention of further damage can lead to better overall health and a reduced need for dialysis.[14]
- **Survival Rates**: Long-term survival rates for pancreas transplant recipients have improved over the years. Advances in surgical techniques, immunosuppressive protocols, and post-transplant care have contributed to extended survival, with outcomes comparable to those of other solid organ transplants.[14]
- **Complications and Adverse Effects**: While pancreas transplantation offers many benefits, it can also involve complications such as organ rejection, infections, and adverse effects related to immunosuppressive medications. Regular monitoring and close collaboration with the healthcare team are essential to manage and mitigate these potential issues.[14]

Challenges in Pancreas Transplantation [15,16]:

- **Organ Shortage**: Like other solid organ transplants, pancreas transplantation faces a shortage of donor organs. This scarcity prolongs waiting times and limits the number of patients who can benefit from the procedure.
- **Rejection:** Despite advances in immunosuppression, graft rejection remains a concern. Striking the right balance between preventing rejection and minimizing immunosuppression-related complications is challenging.
- **Cost and Accessibility:** The financial burden associated with pancreas transplantation, including surgery, immunosuppression, and post-transplant care, can be a barrier for some patients. Ensuring equitable access to transplantation is a challenge.

Current alternatives to Pancreas transplant

- **Insulin pumps**: Continuous subcutaneous insulin infusion (CSII) via insulin pumps was developed in the late 1970s.Continuous subcutaneous insulin infusion infuses insulin continuously at pre- determined basal rates and allows administration of bolus doses for meals and when needed. It is especially useful for T1DM patients who suffer from repetitive hypoglycaemic episodes or have consistently high HbA1C levels despite multiple daily insulin injections. CSII has also been found more effective than multiple daily insulin injections at improving glycaemic control and preventing diabetic ketoacidosis. Limitations of CSII include skin irritation and inflammation at infusion sites, hypoglycaemia due to over-delivery, and risk of diabetes ketoacidosis due to pump failure or cannula occlusion. In addition, patients must regularly monitor their blood glucose level and manually input the food carbohydrate amount into the bolus advisor, to deliver the correct insulin bolus dose. These factors, along with activity restrictions and physical appearance of the pump, may make CSII less appealing to some individuals.[17]

- **Continuous glucose monitors (CGM):**Continuous glucose monitor sensors continuously measure interstitial glucose levels (every 1-5 min) throughout the day, and alert patients when the levels are too low or high. Although CGM performance has significantly improved over the past decade, current sensors are still limited by its accuracy, reliability, and high cost. Continuous glucose monitor sensor–based glucose control outcome, specifically time in range (TIR), is a clinically accepted measure of glycaemic control in T1DM and is accepted by regulatory bodies such as the US FDA as primary outcome of therapeutic efficacy in T1DM studies. Some patients' fear of hypoglycaemia may result in under- dosing insulin or over-correcting hypoglycaemia. Consequently, they remain in a hyperglycaemic state, with increased susceptibility to diabetic complications. [17]
- **Artificial pancreas :** An artificial pancreas refers to AID systems, sometimes known as closed-loop insulin delivery . These systems use a CGM that measures interstitial glucose concentration, an insulin pump, and a control algorithm to calculate insulin dose and maintain normoglycaemia without user input. An artificial pancreas is better able to control blood glucose levels when compared to conventional CSII and maintain near normal nocturnal blood glucose levels. Current AID systems still require user input of carbohydrate amount and pre- meal bolus. Compared to conventional sensor-augmented pump therapy, closed-loop systems are associated with significantly improved TIR and HbA1c levels, without increase in the risk and burden of hypoglycaemia. However, challenges in managing glucose levels after meals and during exercise remain with current closed-loop systems. This is due to the inherent lag in subcutaneous insulin action and sensor glucose (interstitial–vascular glucose transfer lag). [17]
- **Islet cell transplantation:** The incidence of islet cell transplantation have reduced after discovery of insulin. There was a realization that apart from the inconvenience of repeated glucose measurements and insulin injections, many patients still had to face the major complications of diabetes. The regimen followed for islet cell transplantation is "Edmonton Protocol" which consists of transplanting an adequate islet mass sometimes from sequential donors (>10,000 islet equivalents per kg recipient body weight), immediate infusion of the islets following isolation, and avoidance of corticosteroids. As in whole pancreas transplantation, the islets can be transplanted alone or after kidney transplantation.[10,18]

Pancreas Transplant in India :

About 1000 pancreas transplants are performed in the USA each year. In contrast to this, less than 100 such transplants have been performed so far in India. At present, only a few centres across the country offer pancreas transplant on a regular basis including Mahatma Gandhi Medical College & hospital, Jaipur.
The reasons for lack of pancreas transplantation in our country has been the lack of availability of deceased organ donors. This situation is changing fast with over 900 deceased organ donation in last year. Although there is an increase in number of deceased organ donors in India but still the numbers for pancreas transplant are low, this is because unlike kidney and liver, only a small proportion of all donated pancreas' can be used for transplantation, as criteria for pancreas suitability for transplantation are very stringent like age limit between 10-45 years, obesity etc.

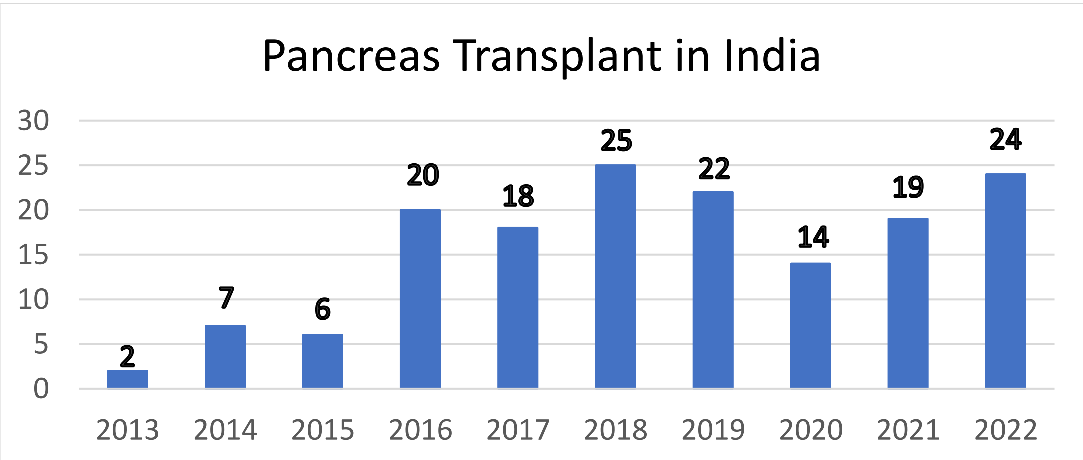

***Figure 2** depicting total number of pancreas transplants in INDIA from 2013-2022. (Chart modified from official registry data of pancreas transplant - ministry of health and family welfare, India)[19]*

Pancreas Transplant from different regions of the world[20]

	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
United States of America	1082	1043	1018	954	947	1013	1002	1027	1015	962	963	–
United Kingdom	236	254	264	239	244	206	202	217	185	116	137	146
Brazil	184	151	163	140	121	134	111	150	177	148	162	133
Germany	171	161	128	120	105	97	72	95	94	92	65	44
Spain	111	83	92	81	97	73	70	82	76	73	82	92
Canada	108	72	77	77	76	95	76	57	69	57	53	–
Argentina	75	68	76	69	74	48	62	89	74	48	39	36
France	73	72	85	79	78	90	96	78	84	34	67	70
Italy	58	67	59	43	50	67	39	41	42	41	54	38
Australia	26	38	33	45	45	51	49	51	40	47	37	–
India	–	–	2	7	6	20	18	25	22	14	19	24

Future Directions in Pancreas Transplantation[3,16,21}:

- **Regenerative Therapies**: Research into regenerative medicine, such as stem cell therapies and islet cell transplantation, aims to restore insulin production without the need for whole pancreas transplantation.
- **Immunomodulation and Tolerance Induction**: Innovations in immune modulation strategies could lead to protocols that induce tolerance, minimizing the need for lifelong immunosuppression.
- **Islet Transplantation**: Islet transplantation, which involves transplanting insulin-producing cells rather than the whole pancreas, continues to evolve with improved techniques and outcomes.
- **Living Donor Pancreas Transplantation**: Advancements in surgical techniques and donor safety measures could make living donor pancreas transplantation a more viable option, reducing the organ shortage.
- **Precision Medicine**: Tailoring immunosuppression regimens based on genetic and immunological profiles could optimize outcomes and minimize adverse effects.
- **Organ Preservation Techniques**: Advances in organ preservation methods, such as machine perfusion, can extend the viability of donor pancreases.
- **Collaboration and Data Sharing**: Collaborative efforts among transplant centers can facilitate the exchange of knowledge, best practices, and data, leading to improved protocols and patient care.
- **Personalized Monitoring and Telemedicine**: Utilizing technology for remote monitoring and telemedicine can enhance post-transplant care and reduce the burden on patients.
- **Xenotransplantation**: While still in experimental stages, xenotransplantation (using organs from animals) holds potential to address the donor organ shortage.

Summary:

To summarize, pancreas transplantation has evolved from experimental beginnings to a transformative treatment for diabetes. The journey of this medical discipline from historical roots to current complexities, challenges, and promising innovations paints a vivid picture of its significant potential. By addressing challenges, embracing innovations, and fostering collaboration, pancreas transplantation holds the power to reshape the landscape of diabetes management and significantly enhance the lives of those affected by this chronic condition.

References:

1. Meirelles Júnior, R. F., Salvalaggio, P., & Pacheco-Silva, A. (2015). Pancreas transplantation: review. *Einstein (Sao Paulo, Brazil)*, *13*(2), 305–309. https://doi.org/10.1590/S1679-45082015RW3163
2. Squifflet, J. P., Gruessner, R. W., & Sutherland, D. E. (2008). The history of pancreas transplantation: past, present and future. *Acta chirurgica Belgica*, *108*(3), 367–378. https://doi.org/10.1080/00015458.2008.11680243
3. Dholakia, S., Oskrochi, Y., Easton, G., & Papalois, V. (2016). Advances in pancreas transplantation. *Journal of the Royal Society of Medicine*, *109*(4), 141–146.https://doi.org/10.1177/0141076816636369
4. Gruessner, R. W., & Gruessner, A. C. (2013). Pancreas transplant alone: a procedure coming of age. *Diabetes care*, *36*(8), 2440–2447. https://doi.org/10.2337/dc12-2195

5. Redfield, R. R., Scalea, J. R., & Odorico, J. S. (2015). Simultaneous pancreas and kidney transplantation: current trends and future directions. *Current opinion in organ transplantation*, *20*(1), 94–102. https://doi.org/10.1097/MOT.0000000000000146
6. Fridell, J. A., Niederhaus, S., Curry, M., Urban, R., Fox, A., & Odorico, J. (2019). The survival advantage of pancreas after kidney transplant. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons*, *19*(3), 823–830. https://doi.org/10.1111/ajt.15106
7. Scalea, J. R., Pettinato, L., Fiscella, B., Bartosic, A., Piedmonte, A., Paran, J., Todi, N., Siskind, E. J., & Bartlett, S. T. (2018). Successful pancreas transplantation alone is associated with excellent self-identified health score and glucose control: A retrospective study from a high-volume center in the United States. *Clinical transplantation*, *32*(2), 10.1111/ctr.13177. https://doi.org/10.1111/ctr.13177
8. Cayabyab F, Nih LR and Yoshihara E (2021) Advances in Pancreatic Islet Transplantation Sites for the Treatment of Diabetes. Front. Endocrinol. 12:732431. doi: 10.3389/fendo.2021.732431
9. Kirchner, V. A., Finger, E. B., Bellin, M. D., Dunn, T. B., Gruessner, R. W., Hering, B. J., Humar, A., Kukla, A. K., Matas, A. J., Pruett, T. L., Sutherland, D. E., & Kandaswamy, R. (2016). Long-term Outcomes for Living Pancreas Donors in the Modern Era. *Transplantation*, *100*(6), 1322–1328. https://doi.org/ 10.1097/TP.0000000000001250\
10. Mehta N Naimish, Sinha Sanjay, Friend Peter, Pancreas Transplantation, Current Pancreatic surgery 2019: 157-178
11. El-Hennawy H, Stratta RJ, Smith F. Exocrine drainage in vascularized pancreas transplantation in the new millennium. World J Transplant. 2016 Jun 24;6(2):255-71
12. Amorese, G., Lombardo, C., Tudisco, A., Iacopi, S., Menonna, F., Marchetti, P., Vistoli, F., & Boggi, U. (2020). Induction and Immunosuppressive Management of Pancreas Transplant Recipients. *Current pharmaceutical design*, *26*(28), 3425–3439. https://doi.org/10.2174/1381612826666200430111620
13. Montagud-Marrahi E, Molina-Andújar A, Pané A*, et al* Outcomes of pancreas transplantation in older diabetic patients *BMJ Open Diabetes Research and Care* 2020;**8:**e000916. doi: 10.1136/bmjdrc-2019-000916
14. Nijhoff MF, Hovens JGFM, Huisman SD, Ringers J, Rabelink TAJ, de Fijter HJW, van der Boog PJM, de Koning EJP. Psychological Symptoms and Quality of Life After Simultaneous Kidney and Pancreas Transplantation. Transplant Direct. 2020 Apr 27;6(5):e552. doi: 10.1097/TXD.0000000000000996. PMID: 32548246; PMCID: PMC7213608.
15. Dholakia S, Mittal S, Quiroga I, Gilbert J, Sharples EJ, Ploeg RJ, Friend PJ. Pancreas Transplantation: Past, Present, Future. *Am J Med.* 2016;129:667–673
16. Cimen SG, Cimen S, Kessaris N, Kahveci E, Tuzuner A. Challenges of pancreas transplantation in developing countries, exploring the Turkey example. World J Transplant. 2019 Dec 20;9(8):158-164. doi: 10.5500/wjt.v9.i8.158. PMID: 31966972; PMCID: PMC6960118.
17. Abdulrahman O Al-Naseem, Ahmed Attia, Ahmed Reda Gonnah, Abdulaziz O A S Al-Naseem, Harry V M Spiers, Angelika Gruessner, Lalantha Leelarathna, Hood Thabit, Titus Augustine, Pancreas transplantation today: quo vadis?, *European Journal of Endocrinology*, Volume 188, Issue 4, April 2023, Pages R73–R87, https://doi.org/10.1093/ejendo/lvad032
18. Anazawa T, Okajima H, Masui T, Uemoto S. Current state and future evolution of pancreatic islet transplantation. Ann Gastroenterol Surg. 2018 Oct 8;3(1):34-42. doi: 10.1002/ags3.12214. PMID: 30697608; PMCID: PMC6345654.
19. https://notto.mohfw.gov.in/WriteReadData/Portal/News/806_1_data_2022.pdf.
20. https://www.transplant-observatory.org/
21. Martin, D.; Alberti, P.; Demartines, N.; Phillips, M.; Casey, J.; Sutherland, A. Whole-Organ Pancreas and Islets Transplantations in UK: An Overview and Future Directions. *J. Clin. Med.* **2023**, *12*, 3245. https://doi.org/10.3390/jcm12093245