

**Review Article**

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Innovative Strategies for Improving Clinical Outcomes in Pancreas Transplantation

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Pancreas transplantation remains the most effective therapeutic option for achieving durable insulin independence and restoring physiological glucose homeostasis in selected patients with complicated type 1 diabetes mellitus. Despite significant advances in surgical techniques, immunosuppressive regimens, and perioperative management, graft thrombosis, rejection, infectious complications, and long-term graft dysfunction continue to limit optimal clinical outcomes. This narrative review summarizes recent innovations that have the potential to improve both short- and long-term outcomes following pancreas transplantation. The review examines advances in donor and recipient selection, including the integration of machine learning algorithms and predictive biomarkers for individualized risk stratification.

Emerging preservation technologies, such as hypothermic and normothermic machine perfusion, are discussed for their role in minimizing ischemia-reperfusion injury and expanding the utilization of marginal donor organs. Contemporary surgical innovations, enhanced perioperative care pathways, and refined anticoagulation strategies are evaluated alongside developments in immunosuppressive therapy, including costimulation blockade, personalized immunosuppression, immune monitoring, and tolerance-inducing approaches. Furthermore, the review highlights the growing role of molecular diagnostics, donor-derived cell-free DNA, transcriptomic profiling, and artificial intelligence-assisted clinical decision support in the early detection of graft injury and rejection. Advances in infection prevention, metabolic monitoring, telemedicine, and multidisciplinary long-term follow-up are also explored as key components of comprehensive patient management.

Finally, promising regenerative medicine strategies, including stem cell therapies, xenotransplantation, bioengineered organs, and gene-editing technologies, are discussed as future directions that may transform pancreas transplantation. By integrating recent technological, immunological, and precision medicine advances, this review provides a comprehensive overview of innovative strategies that may enhance graft survival, reduce complications, improve quality of life, and optimize long-term clinical outcomes for pancreas transplant recipients.

Keywords: pancreas transplantation, donor, CNIs, stem cell, free DNA

Introduction

The world's first successful pancreas transplantation was performed in December 1966 at the University of Minnesota, marking the beginning of a transformative era in the management of type 1 diabetes mellitus. Over the subsequent five decades,

pancreas transplantation has evolved from an experimental procedure to a well-established therapeutic option capable of restoring endogenous insulin production and achieving euglycemia without the need for exogenous insulin administration. For patients with complicated type 1 diabetes—particularly those with

end-stage renal disease, hypoglycemic unawareness, or severe metabolic instability—pancreas transplantation offers not only improved glycemic control but also the potential to halt or reverse the progression of diabetic complications [1].

Despite these remarkable achievements, pancreas transplantation continues to face substantial challenges that limit its broader application and optimal outcomes. The organ shortage remains a critical constraint, with many potential grafts discarded due to concerns about ischemia-reperfusion injury and the quality of marginal organs. Technical complications, particularly graft thrombosis, continue to be a significant source of early graft loss. Immunological challenges, including acute and chronic rejection, pose ongoing threats to long-term graft survival, while the toxicities associated with calcineurin inhibitor-based immunosuppression contribute to both graft dysfunction and patient morbidity [2].

This narrative review aims to provide a comprehensive overview of recent innovations across the entire spectrum of pancreas transplantation—from donor management and organ preservation through surgical techniques, immunosuppressive strategies, post-transplant monitoring, and emerging regenerative approaches. By synthesizing current evidence and highlighting promising developments, we seek to identify strategies that may enhance graft survival, reduce complications, and improve long-term clinical outcomes for pancreas transplant recipients [3].

Historical Context and Evolution of Outcomes

The evolution of pancreas transplantation over the past 50 years provides essential context for understanding current challenges and future directions. A landmark single-center review of 2,500 pancreas transplants performed over more than five decades at the University of Minnesota documented progressive improvements in patient and graft survival across six transplant eras. These improvements were attributed to sequential, overlapping advances in surgical technique, immunosuppressive protocols, reduced preservation times, and more recently, the reduction of immune-mediated graft loss [4].

The overall death-censored pancreas graft half-lives in this cohort were remarkable: >35 years for Simultaneous Pancreas And Kidney (SPK) transplantation, 7.1 years for Pancreas After Kidney (PAK) transplantation, and 3.3 years for Pancreas Transplant Alone (PTA). In the most recent era, 10-year death-censored pancreas graft survival rates reached 86.9% for SPK recipients, 58.2% for PAK recipients, and 47.6% for PTA recipients. Notably, graft loss in SPK transplants was most influenced by patient survival, whereas graft loss in PAK and PTA recipients was more often due to graft failures, highlighting the importance of addressing immunological and technical factors in solitary pancreas transplants [4,5].

Predictors of improved pancreas graft survival identified in this analysis included primary transplants, bladder drainage of exocrine secretions, younger donor age, and shorter preservation time. These findings underscore the importance of optimizing donor selection, preservation strategies, and surgical techniques to

maximize outcomes [6].

Advances in Donor and Recipient Selection

Optimizing Donor Utilization

The persistent gap between organ supply and demand has driven efforts to expand the donor pool through the utilization of marginal donors and donation after circulatory death (DCD) organs. However, less than 64% of donation after brain-death (DBD) and 55% of DCD retrieved pancreases are ultimately used for transplantation. This underutilization reflects concerns about ischemia-reperfusion injury and the quality of marginal grafts [7]. Recent data suggest that normothermic regional perfusion (NRP) in DCD donors can increase pancreas utilization, with promising one-year graft survival comparable to that achieved with DBD donors. This technique allows for in-situ assessment and resuscitation of organs before procurement, potentially expanding the usable organ pool while maintaining excellent outcomes.

Machine Learning and Predictive Analytics

The integration of artificial intelligence and machine learning into donor-recipient matching represents a paradigm shift in transplantation. A multi-agent AI-driven closed-loop optimization system has been developed to systematically identify barriers to pancreas transplant utilization, including low referral rates, complex referral pathways, limited donor availability, and surgical risk concerns. This approach has generated strategic intervention frameworks projected to increase transplant volume by 40% and reduce wait times by 20% by 2022.

AI-enhanced clinical decision support embedded in electronic health records, combined with AI-driven donor-recipient matching algorithms, may enable more precise risk stratification and personalized allocation decisions. These tools have the potential to optimize the use of marginal organs by matching them to recipients with appropriate risk profiles and expected benefits [7].

Predictive Biomarkers for Risk Stratification

Beyond traditional clinical parameters, emerging biomarkers are being evaluated for their ability to predict post-transplant outcomes. In the context of pancreas rejection, machine learning algorithms are being developed to identify patients at risk and potentially detect rejection without performing a pancreas allograft biopsy. Such approaches could facilitate earlier intervention and more personalized immunosuppression management [8].

Innovations in Organ Preservation

Limitations of Static Cold Storage

Static cold storage (SCS) has been the standard method for pancreas preservation for decades, but it has significant limitations. During SCS, tissue oxygenation gradually decreases and eventually reaches zero, contributing to ischemia-reperfusion injury. Moreover, SCS provides no opportunity for organ assessment or therapeutic intervention before transplantation. For the pancreas, which is particularly susceptible to ischemic injury due to its high

metabolic activity and fragility, these limitations are especially problematic [9].

Hypothermic Machine Perfusion

Hypothermic Machine Perfusion (HMP) offers several theoretical advantages over SCS, including the flushing of toxic metabolic byproducts, maintenance of microvascular integrity, delivery of oxygen and nutrients, and replenishment of Adenosine Triphosphate (ATP) stores. Early experiments with HMP were complicated by the development of significant parenchymal edema, which contributed to higher graft loss rates compared to SCS.

However, refinements in perfusion parameters—particularly reducing perfusion pressures to approximately 20 mmHg and optimizing perfusate composition with higher concentrations of oncotic agents—have mitigated these concerns. Preclinical studies in porcine and nonhuman primate models have demonstrated that HMP preserves histological integrity and supports insulin production.

Recent work has focused on the potential benefits of short-term HMP. A controlled DCD porcine model comparing 2 hours of HMP versus SCS before normothermic reperfusion found that HMP significantly reduced resistance indices and improved tissue oxygenation during reperfusion. Importantly, photoacoustic tomography assessment showed no endothelial damage in either group, suggesting that short-term HMP can provide beneficial effects without the edema risks associated with prolonged perfusion [10].

Oxygenated Hypothermic Machine Perfusion

Oxygenated hypothermic machine perfusion (HMPO₂) combines the safety of hypothermia with dynamic perfusion and oxygen delivery to support mitochondrial function and mitigate ischemia-reperfusion injury. In liver transplantation, HMPO₂ has been shown to reduce post-reperfusion syndrome, early allograft dysfunction, and biliary complications. In kidney transplantation, HMPO₂ has been associated with fewer biopsy-proven rejection episodes and lower rates of graft failure compared to HMP alone.

For the pancreas, preclinical studies have demonstrated that HMPO₂ can provide tissue oxygenation and increase tissue ATP levels without the need for perfusate oxygen carriers. In a human split-pancreas model comparing SCS, HMP, and HMPO₂ from both DBD and DCD donors, islet isolation was feasible across all groups, with comparable results. Notably, HMPO₂ of declined human pancreases demonstrated homogeneous perfusion and increased tissue ATP concentration compared to SCS, with no evidence of cellular injury, edema, or reactive oxygen species production after 6 hours of perfusion [10,11].

Normothermic Machine Perfusion

Normothermic machine perfusion (NMP) represents the most physiologic approach to organ preservation, maintaining the graft at body temperature with oxygenated perfusate. NMP offers the potential for functional assessment of grafts before

transplantation, including glucose-stimulated insulin secretion testing to evaluate beta-cell function. Challenges associated with pancreas NMP include the management of pancreatic enzymes in the perfusate and the need for perfusate composition optimized for pancreatic preservation. Nevertheless, NMP provides a platform for therapeutic interventions and viability testing that could enable confident utilization of marginal pancreas grafts for transplantation [12].

Advances in Subzero Preservation

Recent advancements in cryoprotective agent composition, combined with innovative cooling and rewarming technologies, suggest that long-term subzero storage of pancreata and islets may become feasible. Clinical-grade islet vitrification protocols enabling one-year cryopreservation with successful recovery and 90% viability for transplantation have been described. These technologies could revolutionize organ allocation by enabling banking of organs and islets, facilitating better matching, and reducing organ wastage [13].

Surgical Innovations and Perioperative Management

Surgical Technique Refinements

Continuous refinement of surgical methodologies has been fundamental to the evolution of pancreas transplantation. The progressive reduction in preservation times, improved vascular anastomotic techniques, and optimization of exocrine secretion management have all contributed to improved outcomes. Bladder drainage of exocrine secretions, despite its association with metabolic complications, was identified as a predictor of improved graft survival in the University of Minnesota experience, likely reflecting its utility in monitoring for rejection.

In low- and middle-income countries, surgeons have advanced pancreatic transplant surgical techniques with innovative approaches that have reduced complications and improved efficacy. These developments demonstrate the global momentum in surgical innovation for pancreas transplantation [14].

Minimally Invasive Approaches

Initiatives focusing on minimally invasive surgical techniques show potential for enhancing donor organ retrieval, reducing complications, and improving outcomes. While laparoscopic and robotic approaches are more established in other solid organ transplants, their application to pancreas transplantation remains an area of active investigation [14].

Enhanced Perioperative Care Pathways

Enhanced Recovery After Transplantation (ERAT) protocols, adapted from enhanced recovery after surgery (ERAS) principles, are being implemented to optimize perioperative care. These multimodal approaches address pain management, fluid optimization, early mobilization, and nutritional support, potentially reducing length of stay and improving recovery [14].

Anticoagulation Strategies

Graft thrombosis remains one of the most devastating early complications after pancreas transplantation, with reported rates of 5-10%. Refined anticoagulation protocols aim to balance the risks of thrombosis and bleeding, particularly in the immediate postoperative period. The use of dextran, heparin, and antiplatelet agents continues to evolve, with protocols increasingly tailored to individual patient risk factors [15].

Advances in Immunosuppression

Calcineurin Inhibitors: Benefits and Limitations

Calcineurin Inhibitors (CNIs), particularly tacrolimus, have been the mainstay of immunosuppression in pancreas transplantation for decades. However, CNIs are associated with significant toxicities, including nephrotoxicity, beta-cell toxicity, and an increased risk of post-transplant diabetes. Preclinical studies have demonstrated that tacrolimus impairs insulin secretion without affecting cell viability, supporting clinical observations of glucose intolerance and diabetes risk in CNI-treated patients [15].

Costimulation Blockade

Costimulation blockade represents a promising alternative to CNI-based immunosuppression, particularly for pancreas and islet transplantation. Belatacept, a fusion protein that blocks the CD28-CD80/CD86 costimulatory pathway, has been approved for kidney transplantation and is being investigated in pancreas and islet recipients.

In islet transplantation, pilot studies using belatacept-based CNI-free protocols have demonstrated promising outcomes. All five belatacept-treated patients in one series achieved insulin independence after single transplants, with stable renal function and no significant drug-related side effects. Notably, belatacept is not nephrotoxic and has no reported beta-cell toxicity, making it an ideal agent for patients with pre-existing renal dysfunction or unstable diabetes.

However, belatacept-based regimens require careful management to prevent infectious and toxic complications. A regimen of monthly belatacept infusions combined with low-dose tacrolimus in islet transplant recipients effectively prevented donor-specific antibody formation, antibody-mediated rejection, and graft loss, whereas proactive reduction of belatacept dose to 2.5 mg/kg monthly was crucial for minimizing complications and preserving islet graft function.

Other costimulation pathways are also being targeted. CD40-CD40L blockade with agents such as tegoprobart has shown promise in enhancing islet engraftment and reducing insulin requirements in early-phase trials. Investigational biologics targeting ICOS-ICOSL and OX40-OX40L are also being evaluated [16].

Personalized Immunosuppression

The concept of personalized immunosuppression—tailoring regimens to individual patient characteristics, immunological risk, and response—is gaining traction. Immune monitoring approaches

aim to identify patients who may be successfully weaned from CNIs or transitioned to belatacept-based regimens. Late conversion from CNIs to belatacept has been shown to improve HbA1c in kidney transplant recipients with post-transplant diabetes, suggesting potential benefits for pancreas recipients as well [16].

Tolerance-Inducing Approaches

The ultimate goal in transplantation immunology is the induction of operational tolerance, where graft function is maintained without chronic immunosuppression. While clinical tolerance has been achieved in some kidney and liver transplant recipients, it remains elusive in pancreas transplantation. Preclinical studies investigating costimulation blockade, regulatory T-cell therapies, and mixed chimerism approaches may eventually translate to clinical pancreas tolerance protocols [17].

Molecular Diagnostics and Graft Monitoring

Donor-Derived Cell-Free DNA

Donor-derived cell-free DNA (dd-cfDNA) has emerged as a promising noninvasive biomarker for the detection of allograft rejection. In a study of 42 pancreas transplant recipients undergoing for-cause biopsies, dd-cfDNA using a cutoff of $\geq 1\%$ showed sensitivity of 86.7%, specificity of 52.2%, positive predictive value of 54.2%, and negative predictive value of 85.7% in SPK recipients. In PTA recipients, dd-cfDNA perfectly matched biopsy results (100% sensitivity, specificity, PPV, and NPV). The post-treatment trends in dd-cfDNA suggest its potential to guide monitoring and reduce repeat biopsies.

Earlier studies have similarly demonstrated the utility of dd-cfDNA in pancreas transplantation. Using a cutoff of 70 copies/mL, dd-cfDNA showed sensitivity of 85.7% and specificity of 93.7% for detecting rejection in SPK recipients, outperforming traditional markers like lipase and amylase [18].

Transcriptomic Profiling

Beyond dd-cfDNA, transcriptomic profiling of peripheral blood or graft tissue holds promise for more precise assessment of graft injury and rejection. Gene expression signatures associated with rejection, inflammation, and tolerance may enable earlier detection of graft injury before clinically significant dysfunction occurs [18].

Artificial Intelligence in Clinical Decision Support

Machine learning algorithms and artificial intelligence are being developed to identify patients at risk of rejection and to support clinical decision-making. These tools may ultimately enable the detection of pancreas rejection without performing a pancreas allograft biopsy, addressing a significant clinical challenge, particularly for centers without biopsy capability [19].

Infection Prevention and Metabolic Monitoring

Infection Prevention Strategies

Infectious complications remain a significant cause of morbidity and mortality after pancreas transplantation. Immunosuppression increases the risk of bacterial, viral, and fungal infections, while

the presence of the pancreas graft presents unique risks, including intra-abdominal infections and graft pancreatitis. Standard infection prevention strategies include perioperative antibiotic prophylaxis, antifungal prophylaxis, and antiviral prophylaxis for cytomegalovirus (CMV) and Epstein-Barr virus (EBV). Newer approaches include immune monitoring to identify patients at highest risk of infection and preemptive treatment strategies. The use of belatacept has been associated with an increased risk of certain infections, particularly in higher-dose regimens, highlighting the importance of careful monitoring and dose optimization [20,22].

Metabolic Monitoring

Metabolic monitoring is essential for optimizing outcomes after pancreas transplantation. Beyond routine measures of glycemic control, such as hemoglobin A1c and fasting glucose, oral glucose tolerance testing and mixed meal tolerance tests provide more detailed assessment of beta-cell function. These tests can detect early graft dysfunction and guide immunosuppression management [23,24].

Continuous glucose monitoring (CGM) is increasingly being incorporated into the post-transplant care of pancreas recipients, providing real-time information about glycemic patterns and hypoglycemic episodes. CGM data may enable earlier detection of graft dysfunction and more precise insulin management [23,24].

Telemedicine and Multidisciplinary Care

Telemedicine for Post-Transplant Care

The extensive implementation of telemedicine has the potential to augment post-operative care for pancreas transplant recipients. Remote monitoring and consultations can overcome geographical barriers, facilitate timely interventions, and enable collaborative knowledge exchange among specialists. This is particularly valuable for patients in rural or underserved areas who may have difficulty accessing transplant centers for routine follow-up [25-27].

Multidisciplinary Long-Term Follow-Up

Comprehensive long-term follow-up requires a multidisciplinary approach involving transplant surgeons, nephrologists, endocrinologists, dietitians, and mental health professionals. Key components include monitoring for immunosuppression-related toxicities, metabolic complications, and diabetic complications, as well as addressing patient-reported outcomes and quality of life [28,29].

Regenerative Medicine and Future Directions

Stem Cell-Derived Islets

Recent advances in stem cell biology have opened new possibilities for beta-cell replacement therapy. Functional islets can be induced from pluripotent stem cells, including induced pluripotent stem (iPS) cells and embryonic stem (ES) cells. Patient-specific islet cell organoids created from multipotent adult progenitor cells offer the potential for autologous cell replacement, avoiding the need for immunosuppression. Vertex's VX-880

(allogeneic stem cell-derived islet transplant) has demonstrated strong efficacy, with 10 out of 12 patients achieving insulin independence in early trials, leading to progression to phase 3 clinical trials. However, an encapsulated version (VX-264) proved safe but ineffective and was subsequently halted. Other approaches, including gene-edited transplants (Sana's UP421) and induced pluripotent stem cell-derived sheets (Kyoto's OZTx-410), are in various stages of clinical testing [30-32].

Bioengineered Organs

Beyond cellular therapies, bioengineered organs represent a longer-term vision for pancreas replacement. Decellularized organ scaffolds seeded with patient-derived cells could theoretically provide a fully functional, immunologically compatible pancreas. While significant challenges remain, including the complexity of the pancreas architecture and the need for functional vasculature, this remains an active area of investigation [33,34].

Xenotransplantation

Xenotransplantation has received renewed attention following recent advances in gene editing and immunomodulation. Gene-edited porcine islets, modified to reduce immunogenicity and prevent viral transmission, have been evaluated in nonhuman primate models. In a NHP model of porcine islet transplantation, a belatacept-based maintenance regimen combined with a 5c8-containing induction protocol achieved the best functional outcomes and longest graft survival. These studies underscore the central role of rational immunomodulation in advancing clinical xenogeneic beta-cell therapies [35-37].

Gene Editing Technologies

CRISPR-Cas9 and other gene-editing technologies offer the potential to modify both donor organs and recipient immune systems to improve transplant outcomes. Gene editing can reduce the immunogenicity of xenogeneic grafts, eliminate viral sequences, and potentially induce tolerance. For stem cell-derived islets, gene editing may be used to create "universal donor" cells that can be transplanted without immunosuppression [38,39].

Challenges and Future Perspectives

Addressing the Organ Shortage

The shortage of suitable pancreas grafts remains the most fundamental limitation to the broader application of pancreas transplantation. Strategies to address this challenge include:

- Expanded utilization of DCD and marginal donors: Advanced preservation technologies may enable confident utilization of organs currently discarded.
- Ex-vivo organ repair: Machine perfusion platforms may allow for therapeutic interventions that improve graft quality before transplantation [40,41].
- Xenotransplantation: Gene-edited porcine organs could provide an unlimited supply of grafts.
- Stem cell-derived beta cells: Scalable production of functional

islets could eliminate the need for whole-organ transplantation [42-46].

Optimizing Immunosuppression

The ideal immunosuppressive regimen for pancreas transplantation would effectively prevent rejection without nephrotoxicity, beta-cell toxicity, or increased infection risk. Costimulation blockade-based approaches offer promise, but require optimization of induction and maintenance protocols. Immune monitoring and biomarker-guided therapy may enable more personalized immunosuppression, potentially reducing over-immunosuppression and its complications [47-49].

1Overcoming Barriers in Low- and Middle-Income Countries

Pancreas transplantation remains limited in low- and middle-income countries due to facility shortages, lack of specialized personnel, infrastructural deficiencies, and financial constraints. Strategies to address these challenges include enhanced healthcare infrastructure, specialist training programs, international collaborations, and robust funding networks. Telemedicine may play an important role in overcoming geographical barriers and facilitating knowledge exchange [50-51].

Ensuring Equity and Access

As new technologies emerge, ensuring equitable access to pancreas transplantation will be essential. This includes addressing socioeconomic, geographic, and racial disparities in transplant access, as well as ensuring that innovative therapies are accessible to all eligible patients.

Conclusion

Pancreas transplantation has evolved remarkably over the past 50 years, with progressive improvements in patient and graft survival achieved through sequential advances in surgical technique, immunosuppression, preservation, and perioperative care. The most recent era has seen particularly impressive outcomes, with 10-year death-censored graft survival exceeding 85% for SPK recipients in experienced centers [52].

Looking forward, a convergence of innovations across multiple domains promises to further transform the field. Advanced preservation technologies—including HMP, HMPO₂, and NMP—are expanding the usable donor pool and minimizing ischemia-reperfusion injury. Noninvasive biomarkers, particularly dd-cfDNA, are enabling earlier detection of graft injury and more precise monitoring. Costimulation blockade and personalized immunosuppression strategies are reducing toxicity while maintaining efficacy. Artificial intelligence and machine learning are optimizing donor-recipient matching and clinical decision support. And regenerative medicine approaches, from stem cell-derived islets to xenotransplantation, hold promise for ultimately eliminating the limitations imposed by organ shortage [53].

Realizing the full potential of these innovations will require continued investment in research, collaboration across centers, and careful evaluation of emerging technologies through prospective clinical trials. It will also require attention to the

systemic barriers that limit access to pancreas transplantation, including socioeconomic disparities, geographic limitations, and healthcare infrastructure challenges. By integrating recent technological, immunological, and precision medicine advances, the transplantation community can continue to enhance graft survival, reduce complications, improve quality of life, and optimize long-term clinical outcomes for pancreas transplant recipients [54].

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