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Review Article

Current Status and Future Perspectives of Pancreas Transplantation: From Glycemic Control to Immune Tolerance and Regenerative Alternatives

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Abstract:

Pancreas transplantation remains the only established curative therapy for patients with insulin-dependent diabetes mellitus, particularly those with type 1 diabetes and advanced complications. The most commonly performed procedures include simultaneous pancreas–kidney transplantation (SPK), pancreas after kidney transplantation (PAK), and pancreas transplantation alone (PTA). Advances in surgical techniques, immunosuppressive regimens, and recipient selection have significantly improved graft and patient survival rates over the past decades. Despite these improvements, early vascular complications, acute and chronic rejection, and infection remain major challenges. In parallel, emerging alternatives such as islet cell transplantation, stem cell–based therapies, and closed-loop artificial pancreas systems are reshaping the therapeutic landscape. This review summarizes the current status of pancreas transplantation, including indications, outcomes, and complications, and discusses future directions focusing on immune tolerance, bioengineering approaches, and regenerative medicine strategies.

Keywords: Pancreas transplantation; Simultaneous pancreas-kidney transplantation; Type 1 diabetes mellitus; Graft survival; Immunosuppression.

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Introduction

Diabetes mellitus remains a major global health challenge, with type 1 diabetes (T1D) characterized by autoimmune destruction of pancreatic β-cells, resulting in absolute insulin deficiency and lifelong dependence on exogenous insulin therapy.[1] Despite significant advances in insulin delivery systems and continuous glucose monitoring technologies, achieving and maintaining near-physiological glycemic control remains difficult for many patients, particularly those with hypoglycemia unawareness and glycemic variability.[2]

Chronic hyperglycemia is associated with severe microvascular and macrovascular complications, including nephropathy, retinopathy, neuropathy, and cardiovascular disease, which significantly impact morbidity and mortality.[3] In this context, pancreas transplantation represents the only established treatment capable of restoring endogenous insulin secretion, thereby achieving sustained normoglycemia and potentially halting or even reversing diabetic complications.[4]

Since the first successful pancreas transplant performed in 1966, the field has undergone substantial evolution in surgical techniques, organ preservation, immunosuppressive strategies, and patient selection criteria.[5] Currently, pancreas transplantation is primarily performed in three clinical settings: simultaneous pancreas–kidney transplantation (SPK), pancreas after kidney transplantation (PAK), and pancreas transplantation alone (PTA), each with distinct indications and risk–benefit profiles.[6]

Outcomes have improved considerably over the past decades, with advances in immunosuppressive regimens-particularly the widespread use of tacrolimus-based protocols-leading to enhanced graft survival and reduced rejection rates.[7] Nevertheless, pancreas transplantation remains associated with significant early morbidity, including vascular thrombosis, pancreatitis, and infectious complications, which continue to limit its broader application.[8]

Moreover, the therapeutic landscape of diabetes is rapidly evolving. Emerging approaches such as islet cell transplantation, stem cell–derived β-cell replacement therapies, and closed-loop “artificial pancreas” systems are increasingly challenging the role of whole-organ pancreas transplantation.[9]

These developments raise important questions regarding patient selection, long-term outcomes, and the future positioning of pancreas transplantation within diabetes care.

This review aims to provide a comprehensive overview of the current status of pancreas transplantation, including its indications, surgical approaches, outcomes, and complications, while also exploring future perspectives with a focus on immune tolerance, regenerative medicine, and technological innovations.

Types of Pancreas Transplantatıon: Pancreas transplantation can be performed using three principal approaches: simultaneous pancreas–kidney transplantation (SPK), pancreas after kidney transplantation (PAK), and pancreas transplantation alone (PTA). Each modality has distinct indications, benefits, and risk profiles, and appropriate patient selection remains critical to optimizing outcomes.[10]

Simultaneous Pancreas–Kidney Transplantation (SPK): SPK is the most commonly performed type of pancreas transplantation and is generally considered the gold standard for patients with type 1 diabetes and end-stage renal disease (ESRD).[11] This approach offers the advantage of restoring both renal function and endogenous insulin production in a single procedure.

SPK has demonstrated superior patient survival compared to kidney transplantation alone in selected diabetic patients, largely due to improved glycemic control and reduction in diabetes-related complications.[12] Additionally, performing both transplants simultaneously reduces cumulative exposure to immunosuppression and eliminates the need for a second surgical procedure.[13]

Long-term outcomes following SPK are favorable, with reported 5-year pancreas graft survival rates exceeding 70% in high-volume centers.[14] However, the procedure is associated with increased perioperative complexity and early morbidity compared to kidney transplantation alone.[15]

Pancreas After Kidney Transplantation (PAK): PAK involves pancreas transplantation in patients who have previously undergone a successful kidney transplant. This approach is typically considered in patients who either received a living donor kidney transplant or were not suitable candidates for SPK at the time of initial transplantation.[16]

One of the main advantages of PAK is the ability to perform kidney transplantation earlier, thereby reducing time on dialysis and improving overall survival.[17] However, PAK requires a second major surgical procedure and exposes the patient to additional perioperative risks.[18]

Immunologically, PAK may carry a higher risk of rejection compared to SPK, possibly due to prior sensitization and differences in immunosuppressive timing.[19] Despite these challenges, selected patients can achieve excellent metabolic outcomes and improved quality of life.[20]

Pancreas Transplantation Alone (PTA): PTA is primarily indicated in patients with brittle type 1 diabetes characterized by severe glycemic lability, recurrent hypoglycemia, and hypoglycemia unawareness despite optimized medical therapy.[21] Unlike SPK and PAK, PTA is performed in patients with preserved renal function.

The main goal of PTA is to restore normoglycemia and prevent acute metabolic complications rather than to address end-organ failure.[22] However, the risk–benefit balance is more controversial in this group, as patients must accept lifelong immunosuppression without the immediate survival benefit associated with renal transplantation.[23]

Careful patient selection is therefore essential. Current guidelines emphasize the importance of disabling hypoglycemia and impaired quality of life as key indications for PTA.[24]

Patient Selection and Allocation Considerations: Appropriate candidate selection is a cornerstone of successful pancreas transplantation. Factors such as age, cardiovascular risk profile, duration of diabetes, presence of complications, and psychosocial suitability must be carefully evaluated.[25]

Allocation policies vary between regions but generally prioritize SPK candidates due to the combined survival benefit and efficient organ utilization.[26] Advances in donor selection, including the use of extended criteria donors and improved preservation techniques, have expanded the donor pool while maintaining acceptable outcomes.[27]

Surgıcal Techniques and Perıoperatıve Management: Pancreas transplantation is a technically demanding procedure that requires meticulous surgical planning and perioperative management to minimize complications and optimize graft survival.[28] Over the years, refinements in surgical techniques and perioperative care have significantly improved outcomes, although early postoperative complications remain a major concern.[29]

Donor Procurement and Organ Preservation: Successful pancreas transplantation begins with careful donor selection and organ procurement. Ideal donors are typically young, hemodynamically stable, and without significant comorbidities such as diabetes or obesity.[30] However, the use of extended criteria donors has increased in recent years due to organ shortage.[31]

During procurement, the pancreas is retrieved יחד with a segment of the duodenum to facilitate enteric drainage. Preservation solutions such as University of Wisconsin (UW) solution and histidine–tryptophan–ketoglutarate (HTK) are commonly used to minimize ischemic injury.[32] Cold ischemia time is a critical determinant of graft function, with prolonged ischemia associated with increased risk of thrombosis and pancreatitis.[33]

Implantation Techniques: The pancreas graft is typically placed in the right iliac fossa, with systemic venous drainage established via anastomosis to the recipient's iliac vein or inferior vena cava.[34] Portal venous drainage, which mimics physiological insulin delivery to the liver, has also been described and may offer metabolic advantages, although it is technically more complex.[35]

Arterial inflow is usually reconstructed using a donor iliac Y-graft anastomosed to the recipient's common or external iliac artery.[36] Adequate arterial perfusion is essential to prevent graft thrombosis, one of the most feared early complications.[37]

Exocrine Drainage: Enteric vs. Bladder: Management of exocrine pancreatic secretions is a key aspect of surgical technique. Two primary approaches have been used:

- Bladder drainage, historically favored, allows for easy monitoring of urinary amylase levels as a marker of graft function and rejection.[38] However, it is associated with significant urological and metabolic complications, including cystitis, hematuria, and metabolic acidosis.[39]
- Enteric drainage, now the preferred method, involves anastomosis of the donor duodenum to the recipient's small intestine.[40] This approach is more physiological and avoids the complications associated with bladder drainage, although it limits direct biochemical monitoring.[41]

Perioperative Anticoagulation and Thrombosis Prevention

Vascular thrombosis remains the leading cause of early graft loss, occurring in up to 5–10% of cases.[42] Risk factors include donor quality, prolonged ischemia time, and technical issues during anastomosis.[43]

To mitigate this risk, perioperative anticoagulation protocols are widely used, although there is no universal consensus regarding the optimal regimen.[44] Strategies typically include low-dose heparin infusion and early postoperative antiplatelet therapy.[45]

Close monitoring with Doppler ultrasonography is essential in the early postoperative period to detect vascular compromise promptly.[46]

Postoperative Management and Monitoring: Postoperative care focuses on maintaining adequate graft perfusion, preventing infection, and optimizing immunosuppression.[47] Glycemic control is usually achieved rapidly following successful transplantation, often eliminating the need for exogenous insulin within days.[48]

Routine monitoring includes serum glucose, amylase, lipase, and imaging studies when complications are suspected.[49] In enteric-drained grafts, the absence of a simple biochemical marker for rejection necessitates a higher reliance on clinical suspicion and imaging, and in some cases, biopsy.[50]

Early complications include pancreatitis, anastomotic leaks, infections, and bleeding, all of which require prompt recognition and management to preserve graft function.[51]

Outcomes and Survıval: Over the past three decades, pancreas transplantation outcomes have improved significantly due to advances in surgical techniques, immunosuppressive strategies, and recipient selection [52]. These improvements have translated into better short- and long-term graft survival, as well as enhanced patient survival and quality of life.[53]

Patient Survival: Patient survival following pancreas transplantation is generally excellent, particularly in SPK recipients. Reported 1-year patient survival rates exceed 95%, with 5-year survival rates approaching 85–90% in large registry analyses.[54]

Importantly, several studies have demonstrated that SPK transplantation confers a survival advantage compared to kidney transplantation alone in patients with type 1 diabetes and ESRD.[55] This benefit is attributed not only to restoration of renal function but also to improved metabolic control and reduction in cardiovascular risk.[56]

However, early postoperative mortality remains slightly higher in pancreas transplant recipients compared to kidney-alone recipients, reflecting the increased surgical complexity and perioperative risk.[57]

Graft Survival

Pancreas graft survival has also improved substantially over time. Contemporary data suggest:

- 1-year graft survival: ~85–90% (SPK)
- 5-year graft survival: ~70–75%
- 10-year graft survival: ~50–60% [58]

SPK generally demonstrates superior graft survival compared to PAK and PTA, likely due to immunological advantages and more favorable recipient selection.[59]

Early graft loss is most commonly due to technical complications such as thrombosis, whereas late graft failure is typically related to chronic rejection or recurrence of autoimmune processes.[60]

Glycemic Control and Metabolic Outcomes: One of the most compelling benefits of pancreas transplantation is the restoration of endogenous insulin secretion and near-normal glucose homeostasis.[61] Most successful recipients achieve immediate insulin independence, with normalization of HbA1c levels and elimination of severe hypoglycemic episodes.[62]

In addition to glycemic control, pancreas transplantation has been associated with improvements in:

- Lipid metabolism
- Blood pressure regulation
- Endothelial function[63]

These metabolic benefits contribute to the reduction of long-term diabetic complications and improved overall prognosis.[64]

Impact on Diabetic Complications: There is growing evidence that pancreas transplantation may stabilize or even reverse certain microvascular complications of diabetes.[65] For example:

- Diabetic nephropathy: Stabilization of renal function in SPK recipients.
- Retinopathy: Slowing of progression, although early worsening may occur.
- Neuropathy: Partial improvement in nerve conduction over time.[66]

Macrovascular outcomes, particularly cardiovascular disease, also appear to improve following successful transplantation, although long-term data remain heterogeneous.[67]

Quality of Life: Quality of life (QoL) is significantly enhanced following successful pancreas transplantation, primarily due to freedom from insulin therapy and reduced glycemic variability.[68] Patients report improvements in physical functioning, psychological well-being, and social participation.[69]

However, these benefits must be balanced against the burden of lifelong immunosuppression and the risk of complications, which may negatively impact QoL in some patients.[70]

Limitations and Ongoing Challenges: Despite these favorable outcomes, several challenges remain:

- Persistent risk of early graft loss
- Long-term immunosuppression-related toxicity
- Limited organ availability
- Variability in outcomes across centers.[71]

These limitations highlight the need for continued innovation in both surgical and medical aspects of pancreas transplantation.

Complications: Despite significant improvements in surgical techniques and perioperative management, pancreas transplantation remains associated with a relatively high rate of complications compared to other solid organ transplants.[72] These complications can be broadly categorized into early (technical) and late (immunological and metabolic) events, both of which significantly impact graft and patient outcomes.[73]

Early Surgıcal Complıcatıons

Vascular Thrombosis: Vascular thrombosis is the most common cause of early graft loss, occurring in approximately 5–10% of cases.[74] It typically develops within the first postoperative week and may involve arterial or venous occlusion.

Risk factors include donor-related variables (advanced age, obesity), prolonged cold ischemia time, hypotension, and technical issues during vascular anastomosis.[75] Clinically, thrombosis may present with sudden hyperglycemia, abdominal pain, or graft dysfunction, although it can also be asymptomatic.[76]

Early diagnosis using Doppler ultrasonography or contrast-enhanced imaging is critical. In most cases, graft pancreatectomy is required, although early thrombectomy may be attempted in selected cases.[77]

Graft Pancreatitis: Post-transplant pancreatitis is a relatively common complication, ranging from mild self-limited inflammation to severe necrotizing pancreatitis.[78] It is often related to ischemia–reperfusion injury, surgical manipulation, or rejection.[79]

Mild cases are typically managed conservatively, whereas severe forms may lead to graft loss and systemic complications.[80]

Anastomotic Leak and Intra-abdominal Complications: Enteric anastomotic leaks, intra-abdominal abscesses, and bleeding are important early complications that may require reoperation.[81] The shift from bladder to enteric drainage has reduced urological complications but increased the risk of intra-abdominal sepsis.[82]

Prompt recognition and management-including drainage, antibiotics, or surgical intervention-are essential to prevent graft failure.[83]

Infectious Complications: Infections remain a major cause of morbidity and mortality following pancreas transplantation due to intensive immunosuppression.[84] These include:

- Bacterial infections: surgical site infections, intra-abdominal abscesses
- Viral infections: cytomegalovirus (CMV), BK virus
- Fungal infections: Candida species.[85]

The risk is highest in the early postoperative period and during episodes of augmented immunosuppression for rejection.[86] Prophylactic antimicrobial strategies and vigilant monitoring are critical components of postoperative care.[87]

Rejection

Acute Rejection: Acute rejection remains a significant challenge, occurring in up to 15–25% of recipients despite modern immunosuppressive regimens.[88] It may present with hyperglycemia, elevated pancreatic enzymes, or nonspecific clinical findings.[89]

Diagnosis often requires imaging and, in some cases, graft biopsy, particularly in enteric-drained transplants where biochemical monitoring is limited.[90]

Chronic Rejection: Chronic rejection is a major cause of late graft failure and is characterized by progressive fibrosis, vascular changes, and loss of endocrine function.[91] Unlike acute rejection, it is often insidious and less responsive to treatment.[92]

Metabolic and Urological Complications: Bladder-drained grafts are associated with specific metabolic complications, including metabolic acidosis, dehydration, and electrolyte imbalances due to urinary bicarbonate loss.[93] Additionally, urological complications such as hematuria, urethritis, and bladder dysfunction may occur.[94]

Although less common with enteric drainage, metabolic disturbances and gastrointestinal complications can still arise.[95]

Malignancy and Long-Term Risks: Long-term immunosuppression increases the risk of malignancies, particularly skin cancers and lymphoproliferative disorders.[96] Post-transplant lymphoproliferative disease (PTLD), often associated with Epstein–Barr virus infection, represents a serious complication.[97]

Balancing adequate immunosuppression to prevent rejection while minimizing long-term risks remains a central challenge in pancreas transplantation.[98]

Summary of Complication Burden: Overall, pancreas transplantation carries a higher complication rate than most other solid organ transplants, particularly in the early postoperative period.[99] However, with improved surgical expertise, standardized protocols, and multidisciplinary care, these risks can be mitigated, leading to acceptable long-term outcomes in carefully selected patients.[100]

Immunology and Immunosuppressıon: The success of pancreas transplantation is critically dependent on effective immunosuppression to prevent graft rejection while minimizing drug-related toxicity.[101] The pancreas is considered a highly immunogenic organ, and rejection remains a major cause of both early and late graft failure despite advances in immunosuppressive strategies.[102].

Immunological Basis of Rejection: Pancreas allograft rejection involves both cellular and humoral immune responses. T cell–mediated immunity plays a central role in acute rejection, with activation of recipient CD4+ and CD8+ T lymphocytes leading to direct cytotoxicity and cytokine-mediated injury.[103]

In addition, antibody-mediated rejection (AMR) has gained increasing recognition as a contributor to graft dysfunction. Donor-specific antibodies (DSAs) can lead to complement activation, endothelial injury, and microvascular inflammation.[104]

The pancreas is particularly vulnerable to immune-mediated injury due to its rich vascular supply and complex microarchitecture.[105]

Induction Therapy

Induction therapy is widely used in pancreas transplantation to reduce the risk of early acute rejection. Commonly used agents include:

- Anti-thymocyte globulin (ATG)
- Interleukin-2 receptor antagonists (e.g., basiliximab)
- Alemtuzumab (in selected protocols).[106]

Lymphocyte-depleting agents such as ATG are frequently preferred in pancreas transplantation due to the high immunological risk associated with the procedure.[107] These agents provide potent early immunosuppression but may increase the risk of infection and malignancy.[108]

Maintenance Immunosuppression: Standard maintenance regimens typically consist of a triple-drug combination:

- Calcineurin inhibitors (CNIs): most commonly tacrolimus.
- Antimetabolites: mycophenolate mofetil (MMF).
- Corticosteroids.[109]

Tacrolimus-based regimens have largely replaced cyclosporine due to superior efficacy in preventing rejection and improved graft survival.[110]

However, long-term use of CNIs is associated with nephrotoxicity, neurotoxicity, and metabolic side effects.[111]

Steroid minimization or withdrawal protocols have been explored to reduce long-term complications, although their safety remains a subject of ongoing investigation.[112]

Monitoring and Biomarkers of Rejection

Early detection of rejection is critical to preserving graft function. Traditional monitoring methods include:

- Serum glucose levels
- Pancreatic enzymes (amylase, lipase)
- Imaging studies.[113]

However, these markers lack sensitivity and specificity, particularly in enteric-drained grafts. Consequently, there is increasing interest in non-invasive biomarkers, including:

- Donor-derived cell-free DNA (dd-cfDNA)
- Gene expression profiling
- Circulating microRNAs.[114]

These emerging tools may allow earlier and more accurate detection of rejection, potentially improving long-term outcomes.[115]

Chronic Rejection and Immune-Mediated Injury: Chronic rejection remains a major unresolved challenge in pancreas transplantation. It is characterized by progressive fibrosis, vasculopathy, and eventual loss of endocrine function.[116]

The pathogenesis involves a complex interplay between cellular and humoral immunity, as well as non-immunological factors such as ischemia–reperfusion injury.[117] Currently, there are no effective therapies to reverse chronic rejection, highlighting the need for preventive strategies.[118]

Toward Immune Tolerance: Achieving immune tolerance-defined as stable graft function in the absence of long-term immunosuppression-represents the ultimate goal of transplantation.[119] Several experimental approaches are being explored:

- Mixed chimerism via hematopoietic stem cell transplantation
- Regulatory T cell (Treg) therapies
- Costimulatory blockade (e.g., belatacept-based regimens).[120]

Although promising, these strategies remain largely investigational and are not yet part of routine clinical practice [121].

Balancing Efficacy and Toxicity: A central challenge in pancreas transplantation is balancing adequate immunosuppression to prevent rejection with the risk of adverse effects, including infection, malignancy, and drug toxicity.[122]

Personalized immunosuppressive strategies based on immunological risk profiling and biomarker-guided therapy represent a future direction that may optimize this balance.[123]

Alternatıves to Whole-Organ Pancreas Transplantatıon: Although whole-organ pancreas transplantation remains the most definitive method for restoring endogenous insulin production, several less invasive and rapidly evolving alternatives are challenging its role in modern diabetes management.[124] These approaches aim to achieve glycemic control while minimizing surgical risk and the burden of lifelong immunosuppression.[125]

Islet Cell Transplantation: Islet transplantation involves the infusion of isolated pancreatic islets into the recipient's portal vein, where they engraft within the liver and begin insulin secretion.[126] The introduction of the Edmonton protocol marked a major milestone, demonstrating that insulin independence could be achieved without the use of corticosteroids.[127]

Advantages of islet transplantation include its minimally invasive nature and lower perioperative risk compared to whole-organ transplantation.[128] It is particularly attractive for patients with brittle diabetes and hypoglycemia unawareness.[129]

However, several limitations persist:

- Limited availability of donor islets
- Progressive loss of graft function over time
- Requirement for immunosuppression[130]

Long-term insulin independence rates remain modest, although partial graft function can still significantly improve glycemic control and reduce hypoglycemic episodes.[131]

Stem Cell–Derived Beta Cell Therapies: Recent advances in stem cell biology have enabled the differentiation of pluripotent stem cells into insulin-producing β-like cells, offering a potentially unlimited source of transplantable tissue.[132]

These therapies aim to overcome the limitations of donor organ shortage and may allow for standardized, scalable treatment options.[133] Encapsulation technologies are being developed to protect transplanted cells from immune attack, potentially eliminating the need for systemic immunosuppression.[134]

Early-phase clinical trials have shown promising results, with evidence of insulin production and improved glycemic control [135]. However, challenges remain regarding long-term viability, immune protection, and safety, including the risk of tumorigenicity.[136]

Artificial Pancreas Systems (Closed-Loop Technology): Closed-loop insulin delivery systems, often referred to as "artificial pancreas" systems, combine continuous glucose monitoring with automated insulin pumps to provide real-time glucose control.[137]

These systems have demonstrated significant improvements in glycemic control, including:

- Reduced HbA1c levels
- Increased time in target glucose range
- Decreased incidence of hypoglycemia.[138]

Unlike transplantation, artificial pancreas systems do not require surgery or immunosuppression, making them an attractive option for many patients.[139] However, they do not fully replicate physiological insulin secretion and require ongoing patient engagement and device maintenance.[140]

Gene Therapy and Regenerative Approaches: Gene editing technologies, including CRISPR-Cas9, are being explored as potential tools to correct underlying autoimmune mechanisms or to engineer immune-evasive β-cells.[141]

In addition, regenerative approaches aim to stimulate endogenous β-cell regeneration or reprogram other cell types into insulin-producing cells.[142] While still largely experimental, these strategies hold transformative potential for the treatment of diabetes.[143]

Comparative Perspective: When compared to whole-organ pancreas transplantation, these alternative approaches offer several advantages, including reduced invasiveness and potentially lower complication rates.[144] However, none currently match the durability and robustness of glycemic control achieved with successful pancreas transplantation.[145]

As these technologies continue to evolve, the role of pancreas transplantation may shift toward more selective indications, particularly in patients with advanced complications or those unsuitable for alternative therapies.[146]

Future Perspectıves: Despite substantial progress in surgical technique, immunosuppression, and perioperative care, pancreas transplantation remains limited by donor shortage, immunological risk, and procedure-related morbidity.[147] The future of the field is therefore likely to be shaped by innovations in immunology, bioengineering, and precision medicine rather than further incremental surgical refinement alone.[148]

Toward Operational Immune Tolerance: The ultimate goal in pancreas transplantation is the achievement of operational immune tolerance, defined as long-term graft survival without the need for continuous immunosuppression.[149] Current immunosuppressive regimens, while effective, are associated with significant long-term toxicity, including nephrotoxicity, infection, malignancy, and metabolic complications.[150]

Emerging strategies such as regulatory T-cell (Treg) therapy, costimulatory blockade, and mixed hematopoietic chimerism offer promising pathways toward immune tolerance induction.[151] Among these, Treg-based cellular therapies are particularly attractive due to their ability to suppress alloimmune responses while preserving global immune competence.[152] However, translation into routine clinical practice remains limited by manufacturing complexity and variability in response.[153]

Bioengineered and Xenogeneic Organs: Advances in bioengineering and regenerative medicine are expected to fundamentally transform the field of transplantation.[154] Decellularized organ scaffolds repopulated with stem-cell-derived pancreatic cells represent a potential strategy to overcome donor organ scarcity.[155]

Similarly, xenotransplantation-particularly using genetically modified porcine organs-has re-emerged as a viable option due to advances in gene editing technologies that reduce hyperacute rejection and cross-species immune incompatibility (156). Although early experimental results are encouraging, concerns regarding zoonotic infection and long-term graft viability remain significant barriers.[157]

Stem Cell–Based Curative Strategies: Stem cell-derived β-cell replacement therapies may ultimately replace whole-organ transplantation as the preferred curative approach for insulin-dependent diabetes.[158] The development of immune-evasive or encapsulated cell systems could eliminate the need for systemic immunosuppression entirely, representing a paradigm shift in treatment strategy.[159]

However, key challenges persist, including ensuring long-term cellular stability, preventing dedifferentiation, and avoiding uncontrolled proliferation or tumor formation.[160]

Precision Medicine in Transplantation: The future of pancreas transplantation will likely involve a transition toward personalized or precision transplantation medicine.[161] This includes:

- Immunological risk stratification using molecular profiling
- Donor–recipient compatibility beyond HLA matching
- Biomarker-guided immunosuppression adjustment.[162]

The integration of donor-derived cell-free DNA, transcriptomics, and immune monitoring platforms

may allow earlier detection of rejection and individualized therapy adjustment.[163]

Role of Artificial Intelligence and Digital Monitoring: Artificial intelligence (AI) and machine learning are increasingly being applied to transplantation medicine for outcome prediction, rejection risk modeling, and optimization of immunosuppressive therapy.[164]

In parallel, digital health technologies-including continuous glucose monitoring integrated with predictive analytics-are improving long-term metabolic control and may redefine the boundary between transplantation and non-transplant therapies.[165]

Evolving Clinical Indications: As alternative therapies such as artificial pancreas systems and stem-cell therapies improve, the indication spectrum for pancreas transplantation is expected to narrow.[166] Future candidates may primarily include:

- Patients with advanced diabetic complications
- Individuals with combined kidney failure (SPK candidates)
- Cases refractory to all other therapies.[167]

This shift may lead to a more selective, high-risk, high-benefit utilization model rather than broad application.[168]

Concluding Outlook

Pancreas transplantation has evolved from an experimental procedure to a highly specialized therapeutic option capable of restoring physiological glucose homeostasis. However, its long-term future will depend on its ability to integrate or compete with rapidly advancing regenerative and device-based therapies.[169]

Rather than being replaced entirely, pancreas transplantation is likely to coexist within a broader therapeutic ecosystem, serving a carefully selected subset of patients in whom it remains the most effective curative option.[170]

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