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ADVANCES IN ISLET TRANSPLANTATION FOR TYPE 1 DIABETES: FROM CONVENTIONAL METHODS TO STEM CELL-DERIVED THERAPIES

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ABSTRACT

Aim: This review aims to comprehensively evaluate islet transplantation as a treatment for type 1 diabetes mellitus (T1DM), exploring its mechanisms, clinical applications, current challenges, and future potential. Additionally, we explore the potential of stem cell-derived β-cells and the technologies used to differentiate pluripotent stem cells into insulin-producing cells.

Methods: A systematic literature review was conducted using three electronic databases: PubMed, Google Scholar, and Scopus. A total of 71 peer-reviewed articles published between 1979 and 2025 were selected based on keywords such as *islet transplantation, pancreatic islet cells, stem cell-derived β-cells, and immunosuppression*. The analysis primarily focused on the most recent publications, with additional selection criteria including the number of citations and the sample size of the study population.

Results: Islet transplantation is a promising therapy for selected T1DM patients, particularly those experiencing severe glycemic instability. While autologous transplantation following total pancreatectomy effectively preserves endogenous insulin production, allogeneic transplantation remains constrained by donor scarcity and immune-related challenges. The Edmonton protocol has significantly improved graft survival; however, long-term immunosuppression presents considerable risks. Advances in pluripotent stem cell-derived β-cells offer a potential solution to the donor shortage, demonstrating functional insulin secretion in both preclinical and early clinical studies. Alternative transplantation sites, such as the rectus abdominis muscle, have shown promise in enhancing graft viability and function.

Conclusions: Islet transplantation, despite its limitations, remains a viable therapeutic strategy for T1DM patients with poor glycemic control. Stem cell-derived islets represent a breakthrough in overcoming donor shortages, yet further large-scale trials are required to validate their efficacy and safety. Continued research on optimizing transplantation techniques and immunosuppressive strategies will be essential for the future of β-cell replacement therapy.

Keywords: Islet transplantation; type 1 diabetes; β-cell replacement therapy; autologous

transplantation; pluripotent stem cells; immunosuppression; regenerative medicine.

INTRODUCTION

Diabetes is a chronic metabolic disease characterized by a disturbance in glucose homeostasis, leading to an increase in serum glucose levels, known as hyperglycemia [1]. Data published by the World Health Organization (WHO) indicate that in 2022, 890 million people were living with diabetes [2].

In 1979, the National Diabetes Data Group of the NIH introduced a classification of diabetes based on insulin dependency and susceptibility to ketosis. The classification proposed two categories: insulin-dependent diabetes mellitus (IDDM) and non-insulin-dependent diabetes mellitus (NIDDM) [3]. However, this classification is considered outdated and inconsistent with current scientific knowledge. The classification introduced by the WHO in 2019 distinguishes the following categories: type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), hybrid forms of diabetes, other specific types, unclassified diabetes, and hyperglycemia first detected during pregnancy [4]. The two most common types of diabetes are T1DM and T2DM.

Type 1 diabetes accounts for approximately 6% of all cases [5]. T1DM can develop at any age but is most commonly diagnosed between the ages of 10 and 14 [6]. The pathogenesis is rooted in the autoimmune destruction of pancreatic β-cells, leading to a reduction in insulin production and release. Without the regulatory effects of insulin on glucose metabolism, blood glucose levels remain persistently elevated, resulting in the development of diabetes and its associated complications [7].

Type 2 diabetes is the most common form of diabetes, accounting for approximately 90% of cases [8]. The prevalence of T2DM increases with age [9]. Its pathogenesis is complex, with insulin resistance—a state in which the body's cells exhibit an impaired response to insulin—considered a central factor [10]. Risk factors for T2DM include prolonged hyperglycemia resulting from an unhealthy lifestyle and poor dietary habits [11]. Studies have demonstrated a link between a high Body Mass Index (BMI) and an increased risk of developing T2DM [12]. Due to changing lifestyles and the growing obesity epidemic [13], T2DM, previously diagnosed predominantly in adults, is now increasingly affecting children and adolescents [14], a trend likely associated with the rising prevalence of obesity in these age groups [15].

Prolonged elevation of serum glucose levels has serious consequences for the body. Chronic diabetes leads to the development of microvascular and macrovascular complications. Vascular changes result in damage to internal organs, including the eyes (diabetic retinopathy), kidneys (diabetic nephropathy), heart (cardiovascular disease), and brain (cerebrovascular disease) [16]. Strict glycemic control significantly reduces the risk of these complications [17].

Depending on the type of diabetes, different methods are employed to maintain proper glycemic levels. In type 1 diabetes, the cornerstone of treatment is lifelong insulin therapy. Despite advances in diabetes management, such treatment still carries the risk of severe hypoglycemic episodes, prompting researchers to expand their studies in this field [18].

MATERIALS AND METHODS

A systematic literature review was conducted using three electronic databases: PubMed, Google Scholar, and Scopus. A total of 71 peer-reviewed articles published between 1979 and 2025 were selected based on keywords such as *islet transplantation, pancreatic islet cells, stem cell-derived β-cells, and immunosuppression*. The analysis primarily focused on the most recent publications, with additional selection criteria including the number of citations and the sample size of the study population.

RESULTS OF SELECTION AND CONTENT OF THE REVIEW

MOLECULAR MECHANISM OF TYPE 1 DIABETES DEVELOPMENT

The pancreas is an unpaired organ located in the abdominal cavity, which has both exocrine and endocrine functions. The exocrine part is involved in digestion through the secretion of proteolytic enzymes (pancreatic juice)[19]. The endocrine part is responsible for hormonal regulation and is organized into structures known as pancreatic islets or islets of Langerhans. The islets of Langerhans constitute approximately 2% of the pancreatic parenchyma [20]. They are composed of five types of cells: α, β, δ, ε, and PP. Glycemic regulation is primarily managed by α and β cells, which secrete glucagon and insulin, respectively [21]. In an adult human, β cells constitute about 50% of the islet, while α cells make up approximately 40% [22]. These hormones act antagonistically—glucagon increases serum glucose levels by acting on tissues, while insulin decreases it.

The development of T1DM is influenced by immunological, genetic, and environmental components. This means that environmental factors can induce an autoimmune response in genetically predisposed

individuals, ultimately triggering disease onset. Genetic predisposition is associated with polymorphisms in HLA class II genes encoding DQ and DR [23]. Individuals carrying HLA-DRB1*03 (DR3) or HLA-DRB1*04 (DR4) in combination with DQB1*03:02 (DQ8) have the highest susceptibility to developing type 1 diabetes [24,25]. These haplotypes are present in approximately 90% of individuals with T1DM [26].

The main environmental factors suspected of initiating the autoimmune response in T1DM pathogenesis include viral exposure, dietary intake, and the intestinal microbiome [27]. T lymphocytes ($CD4^+$ and $CD8^+$) play a key role in the pathogenesis of T1DM by directly destroying β-cells. Post-mortem analysis of the islets in patients with type 1 diabetes revealed that $CD8^+$ T lymphocytes are the predominant cells in the inflammatory infiltrates near β-cells [28], suggesting their dominant role in β-cell destruction.

Another immunological component involved in β-cell destruction is the presence of anti-islet autoantibodies. These include glutamic acid decarboxylase (GAD) autoantibodies, protein tyrosine phosphatase-related islet antigen 2 (IA-2) autoantibodies, insulin autoantibodies, and zinc transporter Slc30A8 (ZnT8) autoantibodies [29].

In summary, autoimmune mechanisms underlie the development of type 1 diabetes. The loss of properly functioning β-cells within the pancreatic islets disrupts glucose homeostasis. Hyperglycemia occurs when approximately 80% of β-cells are damaged or destroyed, leading to insulin deficiency [30]. Understanding that the reduction in the number of functional β-cells is responsible for T1DM development, islet transplantation appears to be a promising method for managing diabetes, as it can restore insulin independence in selected patients with type 1 diabetes mellitus [31].

METHODS OF ISLET TRANSPLANTATION

Autotransplantation of islets after total pancreatectomy is most commonly performed in patients undergoing complete pancreatic resection due to recurrent acute pancreatitis or chronic pancreatitis [32,33]. During pancreatectomy, the duodenum and spleen are often removed due to their anatomical and physiological connections with the pancreas. Shared blood supply and close anatomical proximity typically necessitate the removal of these structures by the surgeon. After resection, the pancreas is transported to a cGMP or cGTP islet isolation facility, where the process of islet isolation involves several steps. Enzymatic digestion, involving the introduction of digestive enzymes such as collagenase and neutral protease into the pancreatic ducts, breaks down pancreatic tissue, releasing the islets [34,35]. To optimize the process, mechanical techniques such as the Ricordi chamber are utilized to facilitate further separation of islets. The preparation is then subjected to centrifugal purification to separate acinar and ductal tissue from the islets. For autologous transplantation, preparations of lower purity are obtained to minimize islet loss during centrifugation and maximize yield [36] . The final islet preparation is infused into the portal vein through structures such as the splenic vein remnant, mesenteric vein, or recanalized umbilical vein. If a large tissue volume increases portal vein pressure excessively, part of the preparation may be deposited in the peritoneal cavity or other extrahepatic sites [37]

Allotransplantation of islets is performed in patients who have lost islet function, with the primary target population being individuals with type 1 diabetes (T1DM) [38]. In some cases, allotransplantation is also performed in patients who have undergone total pancreatic resection. Allotransplantation involves isolating pancreatic islets from the pancreas of a deceased donor [39]. Islet isolation from living related donors is also possible, but due to the risk of diabetes development in donors and the suboptimal number of transplanted islets under standard immunosuppressive protocols, the procedure's success is limited by graft longevity and is therefore not a recommended method [34,40]. Islet transplantation can be performed using several approaches: Islet Transplant Alone (ITA), which has demonstrated efficacy in glycemic control in patients with β-cell dysfunction. In patients with end-stage renal disease (ESRD), simultaneous islet-kidney transplantation (SIK) may be considered [41].

Alternatively, if the patient has already undergone kidney transplantation, Islet After Kidney (IAK) transplantation may be utilized [42]. Pancreatic islets are suspended in a solution containing human albumin and heparin and then introduced into the portal vein of the recipient via percutaneous or transhepatic approaches or during minilaparotomy [42,43]. Islet transplantation to alternative sites, such as the intestine, spleen, renal capsule, or peritoneal cavity, has also been attempted, though with limited efficacy. After injection, the islets migrate to the liver, where they integrate with the tissue and begin secreting insulin [44].

CLINICAL INDICATIONS FOR ISLET TRANSPLANTATION

Indications for autologous islet transplantation include patients with chronic, persistent pain unresponsive to pharmacotherapy due to chronic pancreatitis, significantly impairing daily functioning, as well as those with recurrent episodes of acute pancreatitis. Non-malignant conditions, such as cysts, calcifications, or other disorders leading to organ failure, also qualify as indications. Rare indications for autotransplantation include pancreatic resection following trauma or benign pancreatic tumors, such as

insulinomas not amenable to enucleation. The high risk of post-operative diabetes associated with total pancreatectomy can be mitigated by autologous islet transplantation. Additionally, successful autotransplantation has been documented following total pancreatectomy due to benign renal cell carcinoma metastases, rescue total pancreatectomy in pancreatic adenocarcinoma, or ampullary carcinoma [34,45]

Patients with severe glycemic control difficulties may benefit from islet transplantation. Allogeneic ITA (Islet Transplant Alone) is indicated in patients with T1DM experiencing frequent hypoglycemic episodes. Despite optimal insulin therapy, such patients suffer from severe hypoglycemic reactions characterized by the absence of warning symptoms and a hypoglycemic threshold below 54 mg/dL. These situations often require third-party intervention for glucose administration or glucagon injection [46].

Simultaneous Islet-Kidney (SIK) transplantation should be considered for patients with T1DM suffering from ESRD and undergoing dialysis. It may also serve as a preemptive transplant option before renal replacement therapy becomes necessary.

Patients with well-functioning transplanted kidneys but persistent glycemic control difficulties may be candidates for IAK (Islet After Kidney) transplantation to prevent the progression of diabetic complications and recurrence of diabetic nephropathy in the transplanted kidney [47]. Both SIK and IAK transplants offer the advantage that recipients are already on immunosuppressive therapy post-kidney transplant. There are no strict indications for choosing between these transplant types; decisions should be made on an individual basis, considering the risk-benefit ratio and specific patient needs.

Islet transplantation requires close collaboration between physician and patient. Psychologically stable patients who can adhere to medical guidelines and manage the challenges of transplantation may be considered for β-cell replacement therapy if they meet the eligibility criteria (Table 1) [48].

Table 1 Eligibility Criteria for Patients Undergoing β-Cell Replacement Therapy

Criterion	Threshold Value
HbA1c	> 7,5–8%
Severe Hypoglycemic Episodes	At least one severe episode per year
Clarke Score	≥ 4
Time in Hypoglycemia (< 3 mmol/L or 54 mg/dL)	> 5% during continuous glucose monitoring (CGM)
Glucose Standard Deviation (SD)	≥ 40 mg/dL
Glucose Coefficient of Variation (CV)	≥ 30%

The updated indications for islet transplantation, established by the Clinical Islet Transplant Consortium, include patients aged 18 to 65 years, regardless of gender. Eligibility criteria require candidates to be psychologically stable and capable of adhering to prescribed medical procedures. Patients must have type 1 diabetes with disease onset before the age of 40, a minimum of five years of insulin dependency, and a combined total of age and diabetes duration of at least 28 years.

Candidates must also exhibit undetectable stimulated C-peptide levels (< 0.3 ng/mL) at 60 and 90 minutes after a mixed-meal tolerance test. Commitment to intensive diabetes therapy is essential, including self-monitoring of blood glucose at least three times daily, the administration of a minimum of three daily insulin injections or insulin pump therapy, and regular care under a specialist (endocrinologist, diabetologist, or diabetes-focused physician) with at least three follow-up visits in the past 12 months.

Additionally, participants must have a documented history of at least one severe hypoglycemic episode within the past year. Such episodes are defined as events resulting in memory loss, confusion, uncontrolled or irrational behavior, difficulty awakening, suspected seizures, loss of consciousness, or other observable symptoms requiring external intervention. During these episodes, blood glucose levels fell below 54 mg/dL, and recovery was achieved following oral carbohydrate administration, intravenous glucose, or glucagon administration.

Furthermore, participants must demonstrate impaired awareness of hypoglycemia, as assessed by specific criteria outlined in the study protocol. These criteria include, but are not limited to, scores from scales such as the Clarke Hypoglycemia Awareness Scale (≥ 4) [49].

IMMUNOSUPPRESSION IN ISLET TRANSPLANTATION

An optimized and effective immunosuppressive protocol is essential to prevent rejection of transplanted pancreatic islets [50]. Both allogeneic and autologous islet transplantation stimulate an immediate innate immune response following islet infusion. However, autologous islets, which are derived directly from the patient, do not carry a risk of immunological rejection or susceptibility to autoimmune damage and therefore do not require immunosuppressive therapy [51].

Early immunosuppressive protocols included induction therapy with thymoglobulin, tacrolimus, mycophenolate mofetil, and high-dose corticosteroids. These agents were toxic to islet cells and caused significant adverse effects in patients. Currently, there is no universally established gold standard for immunosuppressive strategies in human islet transplantation. However, the introduction of the Edmonton protocol, which eliminates corticosteroids and incorporates reduced doses of sirolimus (an mTOR inhibitor that suppresses T-cell proliferation), tacrolimus (a calcineurin inhibitor), and daclizumab (a monoclonal antibody targeting the IL-2 receptor on T-cells), has proven to be an effective regimen, improving islet transplantation outcomes [52].

The Edmonton protocol remains a modifiable framework, with variations across transplantation centers aimed at improving graft survival and reducing the toxicity of the drugs used in the protocol. Belatacept, a costimulation blocker, has emerged as an alternative to tacrolimus, which is toxic to β-cells. Furthermore, the use of belatacept in kidney transplant recipients, particularly in cases of declining eGFR, has been shown to improve HbA1c levels in cases of post-transplant diabetes or de novo diabetes after transplantation [53].

Post-islet infusion inflammation can reduce islet efficacy and survival. To mitigate IBMIR (instant blood-mediated inflammatory reaction), post-operative administration of agents such as TNF-α inhibitors (etanercept), IL-1β blockers (anakinra), and α1-antitrypsin (a serine protease inhibitor that suppresses macrophage activation triggered by interferon gamma) is used to minimize cytokine-induced inflammation [54,55].

To reduce autoimmune responses, agents such as teplizumab and efalizumab, which block T-cell migration, may also be employed. Notably, a protocol incorporating efalizumab (a humanized monoclonal anti-CD11a antibody), daclizumab, tacrolimus, and mycophenolate mofetil has been shown to reduce hepatic inflammation, thereby enhancing islet engraftment [56].

OUTCOMES OF ISLET TRANSPLANTATION

From 2008 to 2023, a group of 114 patients who underwent autologous islet transplantation was evaluated for potential benefits and safety of the procedure. The study included adult patients with fasting blood glucose levels <126 mg/dL and one of the following conditions: painful chronic pancreatitis, significant postoperative pancreatic complications, high-risk pancreaticoduodenectomy, or extensive distal pancreatectomy due to benign or borderline tumors. Among the 114 patients, 19 experienced complications related to the autotransplantation. In 12 patients, complications were due to bleeding associated with portal vein access procedures, but most cases were mild and did not require advanced intervention. Portal vein thrombosis occurred in six patients, and one patient developed a liver abscess. Autologous islet transplantation was successfully performed in 77.6% of cases. Beta-cell graft function following islet autotransplantation (IAT) was assessed using modified IGLS criteria, which classify outcomes into four categories: optimal, good, marginal, and failed, based on HbA1c levels, severe hypoglycemic events, insulin requirements, and C-peptide levels. Optimal graft function was observed in 46.4% of cases, particularly during the first year post-transplant, with a gradual decline over subsequent years. Good function was reported in 14.5% of cases, also primarily in the early post-transplant period. Marginal graft function was noted in 16.7% of cases, showing an increasing trend over time, while failed graft function occurred in approximately 10.8%. The temporal variability in marginal and failed graft function suggests progressive deterioration over time. Patients with optimal graft function were completely insulin-independent with normal metabolic control. Those with good function demonstrated partial insulin independence and good metabolic control. Marginal graft function required higher insulin doses but retained some islet function. In cases of failed graft function, patients remained completely insulin-dependent, with minimal or absent C-peptide production [57].

In another large cohort study of 379 individuals, the function of autologous islet transplants following total pancreatectomy was also evaluated using modified IGLS criteria. Among patients completing a one-year follow-up, 36% achieved optimal outcomes, 37% achieved good outcomes, 24% had marginal outcomes, and 3% experienced failed outcomes [58]. Both studies yielded analogous results, providing comprehensive data on the efficacy and outcomes of IAT, demonstrating both benefits and associated complications of the procedure.

Lehmann et al. conducted a study involving 38 patients who underwent simultaneous islet-kidney

transplantation (SIK) or islet-after-kidney transplantation (IAK). While only 9.3% of patients in the SIK/IAK group achieved insulin-independence post-transplant, long-term follow-up (>10 years) demonstrated sustained glycemic stability and reduced severe hypoglycemic episodes compared to the pre-transplant period. Mean HbA1c levels also improved after transplantation in the SIK/IAK group. C-peptide levels initially remained stable, showing a gradual decline after six years post-islet transplantation. The relaparotomy rate was 10.5%, indicating a low risk of surgical complications, while infusion-related bleeding occurred in 12 cases. Immunosuppressive therapy, particularly sirolimus, was the primary source of side effects, including nephrotoxicity, hematological disorders, and hypercholesterolemia. Severe adverse events were relatively rare [59].

In April 2023, Chetboun et al. published a large multicenter study based on a cohort of 1,210 patients registered in the CITR database. These patients received at least one islet infusion between January 19, 1999, and July 17, 2020. Participants included individuals with type 1 diabetes who underwent allogeneic islet transplantation (ITA) and patients who had received a kidney transplant and at least one islet infusion (IAK). The study focused on determining Primary Graft Function (PGF), measured 28 days after the last islet infusion, calculated as the BETA-2 score using fasting C-peptide levels, glucose levels, and exogenous insulin requirements. A correlation was observed between PGF and the 5-year transplant outcomes, with higher PGF values associated with a reduced risk of adverse outcomes. The mean PGF value for ITA recipients was 13.9 (SD 8.6), while the mean PGF value for IAK recipients was 16.2 (SD 9.5) ($p = 0.002$). The higher PGF scores in the IAK group may result from prior kidney transplantation, requiring adequate immunosuppression [60].

Islet transplantation should be performed after carefully weighing the benefits and risks associated with potential complications. Recent studies and clinical data confirm the safety and efficacy of pancreatic islet cell transplantation for the treatment of type 1 diabetes. Further clinical research will enable the refinement of islet transplantation techniques, maximize β-cell survival, and improve clinical outcomes.

THE USE OF PLURIPOTENT STEM CELLS IN ISLET TRANSPLANTATION

Islet transplantation holds great promise; however, the shortage of material for transplantation significantly hinders the further development of this therapeutic approach. Extensive research is being conducted on the use of pluripotent stem cells (PSCs) in this context. There are two types of PSCs: embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs) [61].

Embryonic stem cells (ESCs) are derived from pre-implantation embryos. These cells have the ability to differentiate into any type of cell or tissue. Their use opens numerous opportunities in biomedicine, particularly in the context of regenerating lost or damaged cells and tissues in degenerative, autoimmune, and genetic disorders [62]. Unfortunately, the use of ESCs has been limited due to increasing ethical controversies [63].

The growing ethical concerns surrounding ESCs have driven researchers to seek alternative sources of cells with properties similar to ESCs. Induced pluripotent stem cells (iPSCs) have proven to be such an alternative. These cells are derived from differentiated somatic cells through reprogramming. Their generation was first described by Takahashi and Yamanaka in 2006. Induced pluripotent stem cells (iPSCs) obtained from fibroblast cultures exhibited the properties of embryonic stem cells and expressed their marker genes [64].

In 2022, a study published in *Nature* described the chemical reprogramming of human somatic cells into chemically induced human pluripotent stem cells (CiPSCs), which exhibit key characteristics of embryonic stem cells. This study proved significant because, unlike the previously used reprogramming methods, chemical reprogramming enables cell fate manipulation in a simple and highly controllable manner [65]. This breakthrough holds potential for maximizing the therapeutic applications of stem cells in biomedicine.

Pluripotent stem cells (PSCs) represent a promising and virtually unlimited source of cells for replacement therapies due to their ability to self-renew and differentiate into various functional cell types. The capacity of ESCs/iPSCs for extensive proliferation and differentiation has drawn researchers' attention to their potential applications in islet transplantation and the treatment of type 1 diabetes (T1D).

TRANSFORMING PLURIPOTENT STEM CELLS INTO INSULIN-PRODUCING CELLS

In 2009, Maehr et al. presented a protocol for generating iPSCs from adult fibroblasts obtained from patients with T1D. The iPSCs were subsequently differentiated into insulin-producing cells. However, these insulin-producing cells lacked several functional characteristics of authentic β-cells. At this stage of research, the efficiency of this process was low, and the differentiation protocol required further optimization [66].

In the following years, numerous studies were conducted to improve protocols for generating stem cell-derived β cells (SC-β cells) to make them as functionally similar as possible to native human islet β-cells.

In 2014, Pagliuca et al., using pluripotent stem cells (PSCs), generated insulin-producing cells that functionally resembled pancreatic β-cells. These stem cell-derived β cells (SC-β cells) exhibited the expression of markers found in mature β-cells and demonstrated comparable functionality *in vitro.*

After transplantation into mice, it was observed that insulin secretion varied depending on blood glucose levels, mimicking the behavior of fully functional pancreatic β-cells. The transplantation reduced hyperglycemia in diabetic mice [67]. The data demonstrate that these cells perform comparably to primary human β- cells both *in vitro* and *in vivo* following transplantation.

In 2022, Yuanyua Du et al. published a study describing the generation of islets from human chemically induced pluripotent stem cells (hCiPSC-islets) and the effects of their implantation into non-human primates. Among the tested subjects, glycemic control parameters improved, and endogenous insulin secretion was restored [68].

FIRST- IN-HUMAN PHASE I CLINICAL TRAIL

The preclinical studies described above led to the point where the first-in-human phase I clinical trial of the transplantation of chemically generated and modified CiPSC-islets was successfully conducted. In October 2024, Wang et al. published a study that detailed the process of generating these cells and the method of their transplantation into a patient. The results of the procedure were then described over a one-year follow-up period. Adipose-derived mesenchymal stromal cells (ADSCs) isolated from the patient's adipose tissue were chemically reprogrammed into chemically induced pluripotent stem cells (CiPSCs). These CiPSCs were subsequently differentiated using a prepared protocol, resulting in cells that replicated the functional potential of human pancreatic islet β-cells. The obtained CiPSC-islets demonstrated insulin secretion capabilities comparable to those of native human islets [69].

Until now, the preferred site for pancreatic islet transplantation has been the portal vein. Unfortunately, this conventional method often leads to complications that may result in graft loss [70,71]. n performing the CiPSC-islet transplantation, Wang et al. opted for an alternative transplantation site to optimize graft survival. Based on prior studies conducted on nonhuman primates [71], instead of infusion into the portal vein, they performed the transplantation into an extraperitoneal location, specifically into the abdominal cavity beneath the anterior sheath of the rectus abdominis muscle [69].

The study conducted by Wang et al. involved a 25-year-old female patient who had been diagnosed with T1DM in 2012 (11 years prior to enrollment in the study). Before joining the study, the patient was on intensive insulin treatment, with an average daily insulin requirement of 54 units. Within two weeks of the transplantation, the patient's need for exogenous insulin began to gradually decrease. By day 75 post-transplantation, the patient achieved complete insulin independence, which was sustained throughout the one-year follow-up period.

Before the transplantation, the parameters reflecting the patient's glycemic control were as follows: over the two years prior to the study, glycated hemoglobin (HbA1c) levels ranged between 7.40% and 8.00%, and during the three months prior to the transplantation, her time-in-range (TIR) was 43.18%. One year after the transplantation, the patient exhibited stable glycemic control, with glycated hemoglobin levels around 5% and a time-in-range exceeding 98%. Additionally, the patient achieved insulin independence and did not experience severe hypoglycemic events [69].

The study by Wang et al. and its results may represent a breakthrough in the approach to islet transplantation and the treatment of patients with type 1 diabetes. However, further research is needed, particularly involving larger patient cohorts and extended observation periods.

CONCLUSION

Type 1 diabetes mellitus (T1DM) is an autoimmune disease characterized by the destruction of pancreatic β-cells, ultimately leading to insulin deficiency and the loss of glucose homeostasis. Islet transplantation represents a promising therapeutic approach for the treatment of T1DM, particularly for patients with difficulty in maintaining glycemic control and recurrent episodes of severe hypoglycemia. Recent advancements, including the development of improved islet isolation techniques, transplantation protocols, and innovative immunosuppressive regimens, have offered significant improvements in patient outcomes and quality of life.

The efficacy of autologous islet transplantation has been demonstrated in preserving β-cell function and preventing post-operative diabetes. Although allogeneic islet transplantation effectively stabilizes glycemia and reduces the frequency of hypoglycemic episodes in T1DM, it remains associated with challenges such as limited donor availability, immunological rejection, and the necessity for lifelong

immunosuppression. Innovative strategies, such as simultaneous islet-kidney transplantation (SIK) and islet-after-kidney transplantation (IAK), have shown the potential to optimize patient outcomes by leveraging existing immunosuppressive protocols.

Despite progress in islet isolation and transplantation techniques, the limited availability of donors remains a major barrier, necessitating the exploration of alternative therapeutic approaches. The development of pluripotent stem cell (PSC)-based technologies, including induced pluripotent stem cells (iPSCs) and chemically reprogrammed PSCs (CiPSCs), offers new possibilities in islet transplantation. Findings from preclinical and early clinical trials demonstrate the feasibility of generating functional islets capable of glycemic regulation. Additionally, the introduction of alternative implantation sites, such as the space beneath the rectus abdominis muscle, has shown promise in improving graft survival and β-cell functionality.

Optimization of PSC differentiation protocols and a deeper understanding of the immune response to transplantation remain critical areas for further research. Islet transplantation utilizing PSC-derived cells has the potential to revolutionize the treatment of T1DM, providing patients with durable improvements in glycemic control and restoration of endogenous insulin secretion. However, the development of technologies involving pluripotent stem cells and their application in islet transplantation requires large-scale, multicenter studies involving larger patient cohorts and long-term follow-up to confirm the efficacy and safety of this approach.

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CONFLICTS OF INTERESTS

The authors declare no conflict of interest

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