# Exploration of Stem Cells in the Treatment of Diabetes

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**Abstract.** Stem cell therapy for diabetes is moving from basic research to clinical validation, bringing new hope for a curative strategy. This article systematically reviews the core progress and challenges in this field. Diabetes is fundamentally characterized by the failure of pancreatic β-cell function, and current therapies cannot reverse the disease course. Stem cells, due to their self-renewal and differentiation potential, have become a key candidate for replacing damaged β-cells. Embryonic stem cells and induced pluripotent stem cells can generate insulin-secreting cells through directed the differentiation, among which the embryonic stem cell route has entered clinical trials and has obtained evidence of functional cure; induced pluripotent stem cells are suitable for individualized treatment, but are hindered by safety and efficiency issues. Mesenchymal stem cells improve the pancreatic microenvironment through immunomodulation and paracrine effects. Multiple meta-analyses have shown that they can significantly reduce glycated hemoglobin and reduce insulin dosage and have good safety. In 2026, a Chinese team reported a study on regenerating islets, which was the first to achieve islet function reconstruction in humans and obtained approval for new drug clinical trials in China and the United States, marking a key step in clinical transformation. However, immune rejection, tumor risk, production standardization, and insufficient long-term efficacy evidence remain major obstacles. In the future, it is necessary to leverage gene editing, metabolic reprogramming, and multi-omics technologies to promote the implementation of individualized and standardized treatment plans and ultimately achieve functional cure of the diabetes.

**Keywords:** Stem Cells, mesenchymal Stem Cells, diabetes, treatment.

## 1. Introduction

Diabetes is a group of metabolic diseases characterized by chronic hyperglycemia. Its essence lies in the deficiency of insulin secretion caused by the dysfunction of pancreatic beta cells, or the resistance of target tissues to insulin action. According to the International Diabetes Federation, the number of global diabetes patients has exceeded 500 million, and the prevalence of adult diabetes in China has risen from 0.67% in 1980 to approximately 12% at present, with a total of 140 million patients, ranking first in the world [1]. According to etiological classification, type 1 diabetes(T1D) is caused by autoimmune attacks that lead to almost complete destruction of beta cells, and patients rely on exogenous insulin for life; type 2 diabetes(T2D) is characterized by the progressive aggravation of insulin resistance and the compensatory decline of beta cell function, and about 30% of T2D patients eventually require insulin treatment.

The current diabetes treatment methods include oral hypoglycemic drugs, insulin injections, and insulin pumps, which can achieve a certain degree of blood sugar control, but they are all "management" rather than "cure" strategies. Exogenous insulin cannot simulate the pulsatile rhythm and glucose concentration-dependent response of physiological insulin secretion, and long-term use faces the risks of hypoglycemia, weight gain, and decreased compliance. More critically, these therapies cannot reverse or delay the progressive loss of beta cell function. For patients with type 1 diabetes, islet transplantation once brought hope for a cure, but the supply of donor pancreases is severely lacking - only about 1,000 surgeries can be performed worldwide each year, which is insignificant compared to the millions of demands [2,3].

In this context, stem cell therapy emerged. Stem cells possess the potential for self-renewal and multi-directional differentiation, theoretically providing an "endless" source of pancreatic β cells. At the same time, they can reshape the pancreatic microenvironment through immune regulation and

paracrine effects. In recent years, from the breakthroughs in in vitro directed differentiation techniques to the clinical validation of pancreatic islet transplantation, the exploration of stem cells in the field of diabetes is undergoing a crucial leap from the laboratory to the bedside. This article will systematically review the research framework and cutting-edge developments in this field from dimensions such as multipotent stem cell differentiation, the application of mesenchymal stem cells, the clinical progress and challenges of pancreatic islet transplantation.

## 2. Pathogenesis of Diabetes

The pancreatic β cells are located within the Langerhans islands of the pancreas and are important cells for regulating blood sugar levels in the body. Under normal circumstances, an increase in blood sugar can stimulate the β cells to secrete insulin, promoting the entry of glucose into peripheral tissues, thereby maintaining stable blood sugar levels. However, during the occurrence of diabetes, the β cells are affected by various factors, including oxidative stress, inflammatory factors, lipid toxicity, and immune attacks, resulting in a decrease in their number or a decline in their function. For type 1 diabetes, the immune system is abnormally activated, and T lymphocytes attack the own pancreatic β cells, causing the β cells to gradually lose their function. Due to the irreversibility of β cell damage, patients usually need to rely on exogenous insulin treatment for life. The development process of T2D is more complex. In the early stage, due to insulin resistance in the body, the β cells compensate by increasing insulin secretion; as the disease progresses, the β cells are in a long-term high-load state, eventually leading to functional failure. Therefore, restoring the number of β cells and improving their function have become important goals in the treatment of diabetes [4-7].

## 3. Classification and Biological Characteristics of Stem Cells

Stem cells are a type of undifferentiated cells that possess the ability to self-replicate and have the potential for multi-directional differentiation. Based on their source and differentiation ability, they can be mainly classified into embryonic stem cells, induced pluripotent stem cells, and mesenchymal stem cells.

### 3.1. Embryonic Stem Cells(ESC)

ESC originate from the inner cell mass of early embryos and possess the ability to proliferate indefinitely and differentiate into cells of the three germ layers, including nerve cells, cardiac muscle cells, and β-like cells of the pancreatic islets. Due to their high differentiation potential, researchers initially attempted to induce the generation of pancreatic β cells using ESCs. By simulating the embryonic pancreatic development process, scientists can regulate ESCs with specific growth factors and signaling pathways to gradually differentiate them into pancreatic progenitor cells and insulin-secreting cells [8].

However, the application of ESCs still has certain limitations. On one hand, the embryonic origin involves ethical controversies; on the other hand, undifferentiated cells may form teratomas, so their clinical application requires strict control.

### 3.2. Induced Pluripotent Stem Cells (iPSCs)

iPSCs are generated through gene reprogramming technology, where mature somatic cells are re-induced to become pluripotent stem cells with characteristics similar to the embryonic stem cells. The iPSC technology has broken through the limitation of traditional embryonic stem cell sources, providing new possibilities for individualized cell therapy.

By preparing iPSCs from patients' own cells and further inducing their formation into pancreatic β cells, the risk of immune rejection can be reduced. Moreover, patient-derived iPSCs can also be used to establish disease models, helping to study the mechanism of diabetes occurrence and screen new therapeutic drugs.

However, iPSCs still face issues such as genetic stability, safety, and insufficient induction efficiency, which require further optimization [8].

### 3.3. Mesenchymal Stem Cells (MSCs)

MSCs mainly originate from the bone marrow, the adipose tissue, the umbilical cord and dental pulp, etc. They have strong immunomodulatory and tissue repair capabilities.

Unlike ESCs and iPSCs, MSCs do not mainly exert their effects by directly differentiating into β cells, but rather by secreting various growth factors and anti-inflammatory factors to improve the pancreatic microenvironment, promote the repair of remaining β cells, and regulate abnormal immune responses.

Due to the characteristics of wide availability of sources, low immunogenicity, and higher safety of MSCs, they have currently become an important direction in diabetes cell therapy research. They are also one of the types of cells most widely used in diabetes cell therapy research [9,10].

## 4. Clinical Research Progress and Key Evidence

Stem cell therapy for diabetes has moved from the laboratory to the clinical validation stage. Two strategies have accumulated data at different levels in the human body.

### 4.1. Therapeutic replacement therapy using pancreatic β cells derived from ESC

Over the past two decades, the differentiation protocols have evolved from immature to mature. The early protocols could only generate "pseudo-β cells" with limited glucose responsiveness; subsequently, researchers developed multi-step directed differentiation strategies by mimicking the microenvironment of embryonic pancreatic development, significantly enhancing cell functionality. In April 2026, the Karolinska Institute team reported an optimized protocol: by adjusting the culture steps and allowing cells to spontaneously form three-dimensional aggregates, high-quality and high-purity insulin-producing cells could be stably prepared from multiple human stem cell lines. These cells responded strongly to glucose stimulation in vitro and gradually matured and effectively regulated blood sugar after transplantation into diabetic mice for several months [11].

In August 2026, researchers discovered that the mitochondrial reactive oxygen species-driven arachidonic acid metabolism axis is a "metabolic checkpoint" that limits endocrine differentiation. By disrupting this pathway through metabolic reprogramming, it can significantly enhance β-cell generation and accelerate functional maturation, providing a new strategy for optimizing ESC differentiation [12].

### 4.2. iPSC and Personalized Therapy Exploration

Recently, a systematic review and meta-analysis included 30 preclinical studies on iPSC-based treatments for diabetes. The results showed that the United States and Japan were leaders in this field, with China ranking third [13]. Although iPSCs have theoretical advantages, their clinical advancement is slower than that of ESCs. As of 2025 statistics, more than a hundred patients have received ESC-derived cell infusions in clinical trials, while iPSC-derived cells have only initiated one clinical trial [14].

This gap mainly stems from the safety concerns specific to iPSCs. The reprogramming process involves genetic manipulation, with the risk of insertional mutations due to gene integration, which may induce tumor formation; moreover, even after differentiation, the residual undifferentiated iPSCs have the potential risk of forming teratomas in the body. How to ensure the differentiation efficiency while completely eliminating undifferentiated cells is a threshold that iPSC clinical transformation must overcome. However, iPSCs have irreplaceable value in disease modeling and drug screening - patient-specific iPSCs can be used to simulate the pathogenesis of diabetes in vitro and screen individualized drugs, and this application direction is more mature than cell transplantation.

### 4.3. Clinical Trials of MSCs: Preliminary Confirmation of Safety

As of 2026, there have been numerous clinical trials of MSCs for treating diabetes completed or ongoing worldwide.

A meta-review systematically integrated 17 systematic reviews and meta-analyses, covering over 8,000 diabetic patients, to assess the efficacy and safety of MSCs in treating diabetes. It showed that MSC significantly improved glycemic control in T2D, with a reduction in glycated hemoglobin of 1.45% and a reduction in insulin requirement of 2.05 U/kg/day; in T1D, the C-peptide increased and the HbA1c decreased, but the improvement in insulin dependence varied. Wharton's jelly and bone marrow-derived MSCs had the best efficacy, while umbilical cord blood-derived MSCs had the poorest effect. Adverse events were mostly mild fever or injection reactions, and serious events were rare and related to combined treatment. The study pointed out that the current evidence is highly heterogeneous, lacks long-term follow-up, and there is an urgent need for standard

A systematic review included 88 high-quality basic and clinical studies, focusing on the effects of UC-MSCs on chronic low-grade inflammation, insulin resistance, and pancreatic β-cell function in T2D. It showed that UC-MSCs inhibited the activation of the NLRP3 inflammasome, reduced pro-inflammatory factors such as the tumor necrosis factor-α and the interleukin-6, promoted polarization of macrophages to the anti-inflammatory M2 type, upregulated the PI3K/AKT signaling pathway, enhanced insulin sensitivity in target organs, reversed β-cell dedifferentiation, inhibited apoptosis, and protected pancreatic function. Clinical studies have confirmed that intravenous infusion of the UC-MSCs can safely reduce the need for exogenous insulin and lower glycated hemoglobin. The core mechanism lies in the inflammation microenvironment-dependent immune regulation, that is, exerting anti-inflammatory effects under high pro-inflammatory factor conditions, restoring immune homeostasis, and thereby delaying the progression of T2DM [16].

### 4.4. Breakthrough Progress in Recombinant Pancreatic Islet Transplantation

In 2026, A study published in the international academic journal The Lancet Diabetes & Endocrinology has reported exploratory clinical research findings on regenerative islet transplantation for the treatment of type 1 diabetes, marking the world's first use of autologous and allogeneic stem cell-derived regenerative islet transplants, respectively. For the first time in the world, they used both autologous and allogeneic stem cell-derived recombinant pancreatic islets for transplantation, achieving the reconstruction of pancreatic islet function and autonomous blood sugar regulation in patients with T1D. This study covered three cases of T1D patients, including the world's first autologous recombinant pancreatic islet transplantation, the world's first allogeneic recombinant pancreatic islet transplantation, and the world's first case of recombinant pancreatic islet transplantation for pediatric T1DM. The longest case has achieved clinical cure for over 26 months. The study was the first to prove at the human level that both autologous and allogeneic recombinant pancreatic islet transplantation can help T1DM patients rebuild pancreatic islet function, autonomously regulate blood sugar, and even get rid of insulin dependence [17].

What is particularly noteworthy is that the "allogeneic human regenerative pancreatic islet injection solution" developed based on this technology has successively obtained the New Drug Clinical Trial (IND) approval from China and the United States in April 2025 and January 2026, becoming the only regenerative pancreatic islet drug globally to have received IND approval from both China and the United States. Currently, it is about to enter the Phase II clinical trial [18]. This indicates that the transplantation of pancreatic islets derived from stem cells is moving from the concept verification in the laboratory to the stage of standardized clinical promotion.

## 5. Challenges in Clinical Translation

Although the prospects are promising, stem cell therapy for diabetes is still a long way from achieving large-scale clinical application.

Immune rejection and autoimmune recurrence are the core obstacles of the cell replacement strategy. Allogeneic transplantation requires long-term immunosuppression, while even for T1D patients, even if they implant their own regenerated islets, the original autoimmune attack tendency still exists. The solutions include immune isolation devices (such as microencapsulation packaging), gene editing to delete HLA antigens, combined infusion of immunomodulatory agents, etc. Currently, microencapsulation transplantation has acceptable results in animal models, but the long-term failure problem caused by fibrotic encapsulation in human trials has not yet been resolved. The risk of tumor formation is the eternal regulatory focus of the pluripotent stem cell route. Even if safer starting points such as endodermal stem cells are adopted, the potential risks of residual undifferentiated cells still need to be backed up through multiple strategies such as strict quality control and suicide gene systems. Large-scale and standardized production involves the construction of the entire chain from cell sources, differentiation processes, quality control standards to cold chain transportation. GMP conditions for large-scale production, maintaining batch-to-batch consistency, and cost control are all thresholds that the productization must cross. Long-term efficacy and safety evidence are also insufficient. The current longest follow-up is only 26 months. Whether the function can be maintained in the long term and whether there are delayed adverse reactions still need larger sample sizes and longer periods of clinical research to answer [19,20].

The future directions can be envisioned from the following aspects: Firstly, the integration of gene editing technology and stem cell therapy, by eliminating immunogenic genes and implanting safety switches, to enhance efficacy and controllability; Secondly, the design of individualized treatment plans assisted by multi-omics and artificial intelligence, to optimize patient screening and treatment plans [12]; Thirdly, the application of new differentiation regulation strategies such as mitochondrial metabolic reprogramming, to increase the production and maturity of β cells [21]; Fourthly, exploring the synergistic effect of stem cell therapy with existing hypoglycemic drugs, and seeking the optimal solution for combined treatment.

## 6. Conclusion

Stem cell therapy for diabetes has made encouraging progress, but there are still systematic obstacles to be overcome before it can be widely applied in the clinical practice. Current evidence indicates that the differentiation protocols of pluripotent stem cells are becoming increasingly mature. In particular, pancreatic β cells derived from embryonic stem cells can now exhibit strong glucose response capabilities in vitro and have demonstrated glucose regulation effects in animal and preliminary human studies. The clinical breakthrough in 2026 for islet transplantation has confirmed that both autologous and allogeneic stem cell sources can reconstruct the islet function of patients with T1D. The longest case has achieved insulin independence for 26 months, and related products have obtained new drug clinical trial approvals in China and the United States, marking the transition of islet transplantation from laboratory concept validation to standardized clinical evaluation. Mesenchymal stem cells have accumulated a large amount of clinical data in improving glucose control in T2D and reducing insulin dependence, but their heterogeneity in efficacy and the optimal cell source and infusion protocol are still unclear, and need to be confirmed through large-scale randomized controlled trials.

However, the clinical translation of stem cell therapy still faces three core challenges: at the biological level, immune rejection and the risk of autoimmune recurrence coexist; even autologous transplantation cannot completely avoid the attack mechanism of the primary disease; microencapsulation packaging, gene editing and other methods are still immature; at the safety level, the tumor risk caused by residual pluripotent stem cells is always a regulatory red line, and a more sensitive quality control and clearance system needs to be established; at the engineering level, the batch consistency of differentiation processes, GMP production costs control and cold chain transportation in the entire chain still require a large amount of investment. In addition, the current

clinical follow-up time is short, and there is a lack of long-term data support for long-term functional maintenance and delayed adverse reactions.

Future research should focus on the following directions: First, integrate gene editing technology into the stem cell differentiation process to construct "universal" seed cells with low immunogenicity and safety switches to reduce the reliance on immunosuppression; second, use single-cell multi-omics and artificial intelligence models to analyze patient subtype differences, design individualized infusion timing, cell dose and combined medication regimens; third, deeply explore new regulatory targets such as mitochondrial metabolic reprogramming, to improve the differentiation yield and functional maturity of β cells at the metabolic level; fourth, systematically evaluate the synergistic effect of stem cell therapy with existing hypoglycemic drugs, explore combined treatment strategies to enhance efficacy and reduce adverse reactions. Only through the close collaboration of basic research, process development and clinical evaluation can stem cell therapy move from "management" to "cure", truly changing the fate of hundreds of millions of diabetes patients.

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