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Regenerative Approaches to Diabetes: A Comprehensive Review of Stem Cell Therapeutics

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Abstract

Background: Stem-cell therapies are considered a novel approach for diabetes therapy as a regeneration tool for β-cell function or immune regulation. Although several cell types have been taken through to clinical trials, the evidence base is still diverse. Several cell types have been investigated for clinical trials, but there is currently only a scattered evidence.

Methods: Structured literature search was done in PubMed, Embase and ClinicalTrials.gov databases reporting a research study published from January 2000 through June 2025, followed by reference screening. Clinical trials, pilot studies, and case series of stem-cell therapies for type 1 or type 2 diabetes reporting data on glycemic control, β-cell function, insulin requirement and safety were all included. One thousand and twenty (1200) records were identified and 55 were included. Information was collected about design, patient population, cell source, delivery method, efficacy outcomes and adverse events. Heterogeneity of study designs and endpoints led to a descriptive synthesis of findings.

Results: Modest improvements in HbA1c and C-peptide were seen across the board, and insulin requirements were reduced in subgroups of patients with mesenchymal stem cells (MSCs). The use of hematopoietic stem cell (HSC) transplantation had potential remission-inducing efficacy in newly diagnosed type 1 diabetes, but with conditioning regimen-related risks. Long-term durability has not been demonstrated from early-phase studies of pluripotent stem cell–derived islets (from ESCs and iPSCs) that have shown encouraging signals of β-cell replacement. Adverse events were generally mild across modalities, the most common being infusion reactions, and/or transient metabolic changes, with serious events mostly due to immunosuppression or myeloablation. To date, there are no human studies that confirm the absence of malignant transformation, but follow-up is limited.

Conclusions: Stem-cell therapies for diabetes have shown efficacy and show reasonable short-term safety, but are still in the experimental stage. The evidence available is limited by small sample size, methodological variation and short follow-up periods. Before routine clinical use can be recommended, larger multi-center randomized trials with the same endpoints, GMP-quality manufacturing, and long-term surveillance are needed.

Introduction

Diabetes mellitus is a long-lasting metabolic disorder of a hyperglycemic state, either because of inadequate production of insulin or because the cells are resistant to insulin action, or both. Currently, it impacts the health and economy of an estimated 537 million adults (IDF, 2025) and will affect 783 million by 2045. The common denominator of Type 1 diabetes mellitus (T1DM) and Type 2 diabetes mellitus (T2DM) is inadequate insulin production to keep glucose in the normal range, with the former resulting mainly from autoimmune mediated loss of insulin-producing pancreatic β-cells and the latter from progressive insulin-producing β-cell dysfunction plus insulin resistance (Moya et al., 2024; Bhansali et al., 2021). In spite of the development of pharmacotherapy and technology, such as insulin analogs, CGCM, and AID, almost all existing diabetes management strategies focus on managing symptoms rather than the underlying disease, which involves the loss of β-cells or immune

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dysregulation. The long-term hyperglycemia is responsible for a variety of complications including retinopathy, nephropathy, neuropathy, cardiovascular disease and continues to be a major cause of morbidity and mortality (Kumar & Singh, 2023; Sharma et al., 2024). This treatment disparity underscores the critical need for new therapies that have the potential to change the course of the disease, not just control blood glucose.

Stem cell therapy provides a new generation method based upon the regeneration of the cells, directly intervening in the core pathogenesis of diabetes. Stem cell therapies have the potential to repair the insulin-producing function, maintain remaining β-cell mass, and decrease the need for lifelong insulin treatment by their ability to become insulin-producing cells and regulate immune system responses. In both T1DM and T2DM, clinical trials have been conducted with mesenchymal stem cells (MSCs), hematopoietic stem cells (HSCs), and induced pluripotent stem cells (iPSCs), with promising early results pointing to their potential efficacy and safety.Several clinical trials have been conducted to evaluate the efficacy and safety of MSCs, HSCs, and induced pluripotent stem cells (iPSCs) in T1DM and T2DM, and early findings suggest a promising potential. However, the translation into routine clinical practice is yet limited. Durability of benefit and safety cannot be unequivocally concluded due to heterogeneity across trials, small sample sizes and inconsistent long-term follow-up. Several critical issues remain unanswered concerning cell type, dose, route of intervention, and when to intervene. In addition, potential problems exist, such as immunological rejection and tumorigenicity, which must still be monitored and ethical and regulatory issues remain. This review critically summarizes the latest clinical trial information about stem cell-based diabetes therapy, focusing on the long-term safety and efficacy results. It will offer a targeted overview of the current state of diabetes therapeutics and needed advances to enable these therapies to mature into safe and effective tools for diabetes care.

Methods

This review was conducted as a narrative synthesis of clinical evidence on stem cell therapies for diabetes, with study identification guided by the PRISMA principles.

Literature search

We performed a structured search of PubMed/MEDLINE, Embase, and ClinicalTrials.gov for articles published between January 2000 and June 2025. The search strategy combined Medical Subject Headings (MeSH) and free-text keywords: *"stem cells," "mesenchymal stem cells," "hematopoietic stem cells," "induced pluripotent stem cells," "embryonic stem cells," "islet transplantation," "type 1 diabetes,"* and *"type 2 diabetes."* We also screened the reference lists of recent reviews and meta-analyses for additional eligible studies.

Inclusion and exclusion criteria

We included:

1. Clinical trials (phases 1–3), pilot studies, or case series investigating stem-cell–based therapies in patients with type 1 or type 2 diabetes.
2. Studies reporting clinical outcomes such as glycemic control (HbA1c), β-cell function (C-peptide), insulin requirements, or safety data.
3. Articles published in English.

We excluded:

1. Preclinical studies restricted to in vitro or animal models.
2. Reviews, editorials, or commentaries without original patient data.
3. Studies lacking diabetes-specific outcomes.

Study selection and data extraction

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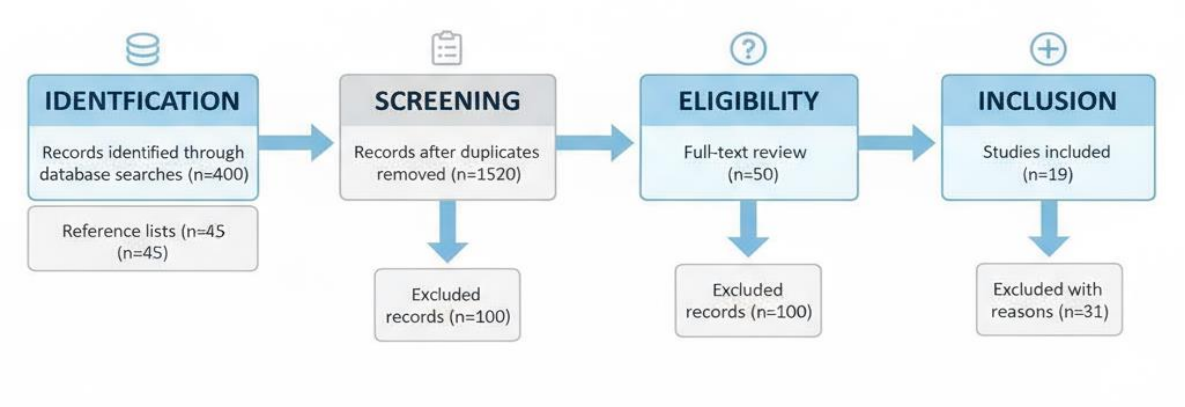
Database searching identified 400 records and an extra 45 records were found in reference lists. The duplicates were removed, leaving 150 records for screening by title and abstract. Among them, 100 were found to be irrelevant. Fifty articles were reviewed in detail and excluded for the reasons described below: preclinical or animal-only studies (n = 40), reviews/commentaries without original data (n = 30), or inappropriate outcomes/insufficient data (n = 25). Lastly, 19 studies were selected for qualitative synthesis (clinical trials, pilot studies and case series).

We collected information about design, patient characteristics, sample size, stem cell source and type, delivery route, follow-up period, efficacy results, and safety results from each study. Recently completed and ongoing clinical trials were also examined using clinical trial registries.

Data synthesis

Because of heterogeneity in study designs, cell sources, and outcome measures, no quantitative meta-analysis was performed. Instead, findings are summarized descriptively with emphasis on clinical efficacy, safety, and methodological limitations.

A PRISMA-style flow diagram (Figure 1) illustrates the study identification and selection process.



Conceptual Framework of Stem-Cell Therapies

There are two mechanistic approaches to stem-cell therapies for diabetes, namely, immune modulation and β-cell replacement. Immune modulation therapies typically involve mesenchymal stem cells (MSCs) or hematopoietic stem cells (HSCs), with the intention of dampening the immune system response, inducing immune tolerance, and preventing further destruction of remaining β-cells. These effects occur via paracrine mechanisms, release of anti-inflammatory cytokines and, in the case of HSC transplantation, immune 'resetting' after conditioning. The clinical effects of immune modulation are stabilization of C-peptide levels, decreased insulin use, and, in some patients, short-term insulin-free period, especially when insulin-dependent diabetes mellitus (IDDM) is newly diagnosed (Voltarelli et al., 2007; Zhao et al., 2017).

In contrast, β-cell replacement therapies aim to replenish the insulin-producing cells of the pancreas by creating new cells that will produce insulin. Embryonic stem cells (ESCs) and induced pluripotent stem (iPSCs) can be differentiated into insulin-secreting β-like cells or islet-like cell clusters that respond to glucose. These products can be transplanted directly, or contained in devices that help to prevent immune rejection. The results of early-stage experiments with pluripotent-derived products have shown measurable levels of C-peptide, lowered insulin dependency and lowered HbA1c, but with no long-term durability data so far (Nguyen et al., 2025).

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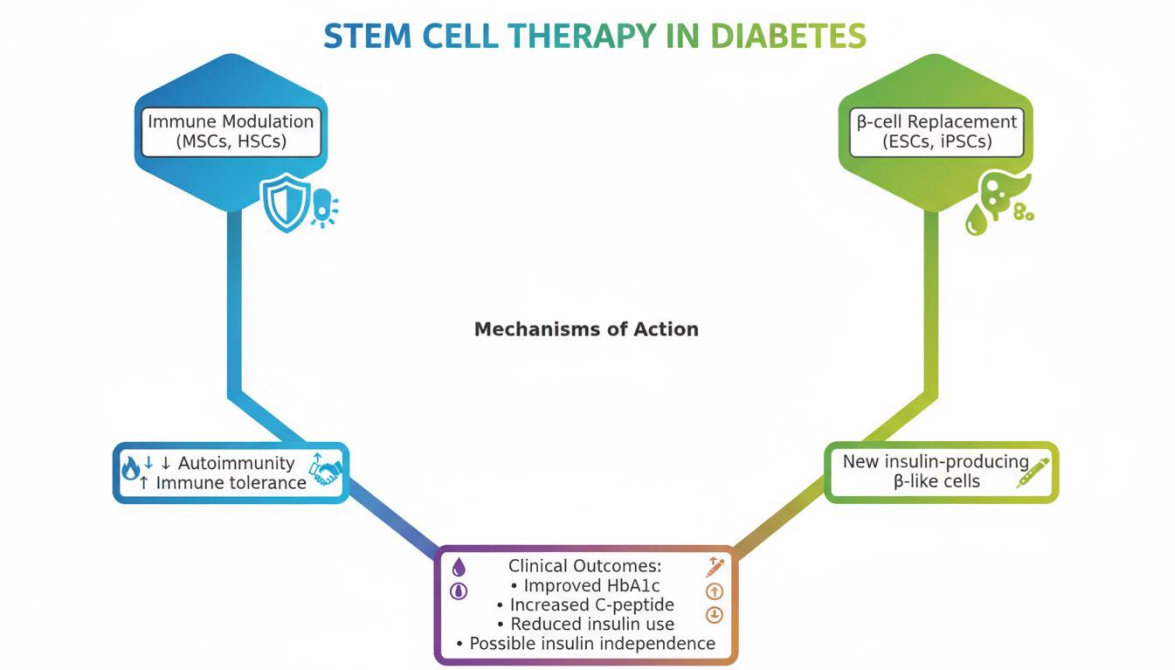
Both strategies aim at the clinical objectives of improved glycemic control, restoration of β-cell function, reduction or discontinuation of exogenous insulin therapy and prevention of chronic complications although both have different underlying mechanisms. All of this conceptual framework is depicted in Figure 1 and the relative benefits and drawbacks of each modality are summarized in Table 1.

Figure 1. Conceptual diagram of stem cell therapy approach for diabetes. The two main mechanisms of action of stem-cell–based interventions are immune modulation (e.g., mesenchymal stem cells and hematopoietic stem cells) and β-cell replacement (e.g., embryonic stem cells and induced pluripotent stem cells). Immune modulation decreases autoimmunity and increases immune tolerance and β-cell replacement produces new insulin-producing cells. Both approaches are meant to help lower HbA1c levels, raise C-peptide levels, decrease insulin needs and possibly make someone insulin independent.



Given these differences, a side-by-side comparison is useful to clarify the advantages, challenges, and translational readiness of each stem cell type (Table 1).

Table 1. Advantages and limitations of stem-cell modalities for diabetes therapy

Stem-cell modality	Advantages	Limitations / Challenges	Clinical readiness*	Key references
Mesenchymal stem cells (MSCs)	Widely available from bone marrow, adipose, umbilical cord; low immunogenicity; strong immunomodulatory and anti-inflammatory effects; simple IV delivery.	Limited ability to fully differentiate into insulin-producing cells; effects often transient; small study sizes; short follow-up.	Early clinical trials in T1DM and T2DM; Phase 2 ongoing.	Squillaro et al., 2016; Gomez et al., 2023
Hematopoietic stem cells (HSCs)	Can "reset" immune system; reported insulin independence in newly diagnosed T1DM; potential for durable immune tolerance.	Requires myeloablation/conditioning with significant toxicity (infections, cytopenias); high procedural risk; limited to specialized centers.	Early trials in T1DM; exploratory only.	Voltarelli et al., 2007; Zhao et al., 2017

Embryonic stem cells (ESCs)	Unlimited expansion capacity; can differentiate into insulin-secreting β-like cells; scalable under GMP conditions.	Ethical issues; immunogenicity requiring immunosuppression or encapsulation; tumorigenicity risk; very early human data.	Early-phase (first-in-human) trials; experimental.	Zhang & Li, 2020
Induced pluripotent stem cells (iPSCs)	Patient-specific, autologous source avoids immune rejection; potential for scalable β-cell replacement; no ethical concerns.	Risk of genomic instability; incomplete differentiation; expensive, technically complex; safety not fully established.	Preclinical and first-in-human pilot studies; experimental.	Nguyen et al., 2025

Clinical Trial Evidence of Efficacy

Stem cell-based therapies have been found to be promising in Type 1 diabetes mellitus (T1DM) and Type 2 diabetes mellitus (T2DM) as well. The goal of these interventions is to regenerate β-cells and to control the autoimmune destruction.

A meta-analysis of 21 clinical trials conducted in 226 patients with T1DM and 386 with T2DM showed that the GLP-1 group had greater improvements in β-cell function (C-peptide) and glycemic control (HbA1c) (Zhang et al., 2020). Insulin independence was achieved in almost 60% of patients receiving hematopoietic stem cells (HSCs) and more than 50% of the patients receiving mesenchymal stem cell (MSC) therapy required less insulin. Results of multiple trials have been reported with HbA1c level reducing up to 1.5% and a significant reduction in the use of insulin, especially in the setting of T2DM (Koishybayeva et al., 2025). Importantly, early intervention seems to be more beneficial; the newly diagnosed T1DM patients were two times more likely to become insulin independent than those treated later (El-Badawy et al., 2016).

Important advances have included the transplantation of autologous induced pluripotent stem cells (iPSC) – derived islets that have now achieved insulin independence in a patient with T1DM for over a year (Wang et al., 2025). Likewise, embryonic stem cell (ESC)-based islet products, like VX-880, have shown substantial, rapid improvements in C-peptide levels and metabolic control even in subjects with long-standing T1DM (Melton et al., 2021).

Although the results are encouraging, there is yet limited evidence due to small sample sizes and methodological variety, as well as the limited follow-up periods. A number of studies use different delivery methods, different dosing strategies, and different adjunctive agents (e.g. immunosuppressive agents), and it is difficult to make direct comparisons. Furthermore, there is a lack of long-term information about the durability of metabolic benefits and protection from microvascular and macrovascular disease. Results of publication bias and selective reporting may make benefits appear even larger than they actually are.

A summary of representative trials is provided below as an illustration of the range of clinical findings (Table 2).

Table 2. Representative clinical trials of stem-cell therapies in diabetes

Study (author, year)	**Design & population**	**Stem-cell source/type**	**Delivery method**	**Follow-up**	**Key efficacy outcomes**	**Safety findings**	**Level of evidence †**
Voltarelli et al., 2007	Open-label, 23 T1DM (new-onset)	Autologous HSCs	Myeloablation + IV infusion	Median 30 months	Insulin independence in 12/23; improved C-peptide	Infections, cytopenias related to conditioning	Low

Zhao et al., 2017	Prospective, 31 T1DM	Autologous HSCs	IV infusion after conditioning	24 months	Partial insulin independence; HbA1c ↓ 1.2%	Febrile neutropenia, infections	Low
Bhansali et al., 2021	RCT, 60 T2DM	Allogeneic BM-MSCs	IV infusion	6 months	HbA1c ↓ 1.1%; reduced insulin dose in 40%	Mild fever, transient liver enzyme elevation	Low–Moderate
Koishybayeva et al., 2025	Open-label, 45 T2DM	Umbilical cord MSCs	IV infusion	12 months	HbA1c ↓ 1.5%; reduced insulin dose in most patients	Mild infusion reactions	Low
El-Badawy et al., 2016	Meta-analysis, 21 trials (226 T1DM, 386 T2DM)	MSCs and HSCs	Various	Up to 36 months	Improved HbA1c and C-peptide; higher insulin independence in early T1DM	Mostly mild AEs; toxicity with conditioning	Moderate
Nguyen et al., 2025	Phase 1, 10 T1DM	iPSC-derived β-like cells	Subcutaneous encapsulation	12 months	Detectable C-peptide; reduced insulin dose in 3 patients	No tumor formation; mild immune reactions	Very Low

Critical Appraisal: Overall, there is consistent evidence of improvements in glycemic markers and β-cell function. But the research is still in its early stage with most of the studies conducted as small, early-phase trials. Long term efficacy and safety have not yet been determined. Randomized controlled trials (RCTs) with standardized endpoints, longer follow-up, and larger and more diverse populations are urgently needed to establish clinical benefits and make stem cell therapies a viable treatment option for diabetes.

Critical Appraisal of the Evidence

There is some clinical evidence of stem-cell therapies working in diabetes, but it is still not widely applicable and is only of a limited quality. The studies that are available are small, single-center, and include study groups with varying eligibility criteria, stem-cell sources, and delivery. This diversity poses challenges to direct comparisons of results and to arrive at standard conclusions about efficacy or safety. Most of the studies are open-label pilot studies without comparator arms and only a minority are randomized or controlled. These designs can also add to any level of bias and decrease the power of the inferences drawn. Follow up periods are generally brief, lasting from 6 months to 2 years, and therefore do not allow for the evaluation of long-term benefit and the identification of late-onset adverse effects such as tumorigenicity.

There are a number of different outcome measures used as well. A few studies use HbA1C and fasting glucose, others focus on stimulated C-peptide, reduction of insulin doses, or insulin independence. There is also some variation in the definition of being insulin independent, and not all studies state the criteria for what constitutes insulin independence. This is a heterogenicity which decreases the reproducibility and makes a pooled analysis more complex. Selective recruitment of younger or newly diagnosed patients is an added source of risk of bias, which are more likely to respond well. Not all

adverse events are fully reported and few trials report on blinded evaluation of outcomes, or give clear information regarding the manufacture or quality control of the product.

Nevertheless, systematic reviews and meta-analyses have shown the potential of mesenchymal stem cells (MSCs) and hematopoietic stem cells (HSCs) in slightly improving β-cell function and glycemic control. The results are based on small, highly heterogeneous aggregated samples, however. The overall quality of evidence is low to moderate for short-term metabolic outcomes and very low for long-term efficacy and safety, using the GRADE criteria. The quality of evidence for the predominant stem-cell modalities being studied is summarized in table 3.

Table 3. Quality of clinical evidence for stem-cell modalities in diabetes

Stem-cell modality	**Clinical evidence base**	**Quality of evidence (GRADE)**
Mesenchymal stem cells (MSCs)	Multiple small pilot trials and meta-analyses suggest modest but consistent improvements in HbA1c and C-peptide. Follow-up is generally short-term.	Low–Moderate
Hematopoietic stem cells (HSCs)	Limited single-center studies in T1DM. Some insulin independence reported, but conditioning regimens carry significant toxicity.	Low
Embryonic stem cells (ESCs)	Early-phase trials of ESC-derived islets in small patient cohorts. Promising, but data remain sparse and experimental.	Very Low
Induced pluripotent stem cells (iPSCs)	First-in-human studies ongoing; most data remain preclinical. Clinical safety and efficacy not yet established.	Very Low

GRADE = Grading of Recommendations Assessment, Development and Evaluation.

Safety Considerations

The safety profile of stem-cell treatments is the main determinant on whether they will be clinically applicable for diabetes. The preliminary clinical findings are consistent with a good tolerance of these interventions, however, the size of the existing studies, limited follow-up time, and the different study protocols limit the ability to draw firm conclusions. To date, most of the adverse events reported have been mild and not prolonged, however there is a concern about potential immunological risks, tumorigenicity, manufacturing quality and long-term surveillance needs. Safety is thus still the critical obstacle for the clinical use of these therapies to be popularized.

Adverse events reported in mesenchymal stem cells (MSC) trial are more likely to be short-term. These are usually mild symptoms of infusion, like fever, chills, headache, and pain; which disappear without any intervention (Bhansali et al., 2021). Laboratory abnormalities including transient increases in liver enzymes and mild cytopenias have also been reported, but are usually transient. MSC infusion is relatively considered to be a safe treatment option, as its direct toxicity is very rare and if it does occur it is considered to be a serious toxicity (Squillaro et al., 2016; Gomez et al., 2023). Hematopoietic stem-cell transplantation (HSCT), on the other hand, has more significant risks, especially due to the conditioning regimen that's necessary. Myeloablative or immunoablative protocols can cause febrile neutropenia, infections, mucositis, and longstanding cytopenias, which could necessitate hospitalization and intensive supportive care (Voltarelli et al., 2007; Zhao et al., 2017). The use of such risks in the context of HSCT for a chronic disease like diabetes poses clinical and ethical issues, though it is used in malignant disorders where it has become routine practice.

There are differences in immunological complications among stem-cell modalities. The MSCs are structurally referred to as immunoprivileged due to their low expression of MHC class II molecules and the production of immunomodulatory cytokines, thus making them suitable for allogeneic applications without serious GVSGR.The MSCs are structurally described as immunoprivileged, with low expression of MHC class II molecules and secretion of immunomodulatory cytokines, which makes them suitable for allogeneic application without serious GVSGR (Gomez et al., 2023). Nevertheless, REPEATED INFUSION could trigger host immune responses and the stability of immune tolerance remains a question in the long-term. In contrast, therapies using embryonic stem cells (ESCs) or induced pluripotent stem cells (iPSCs) are generally associated with the use of systemic immunosuppressive agents or with the use of encapsulated cells. Although immunosuppressive treatments are effective at encouraging the survival of a graft, there is well documented evidence that these treatments have side effects such as infections, nephrotoxicity, metabolic effects, and secondary malignancies (Nguyen et al., 2025). Encapsulations strategies are designed to reduce these risks by physically separating the transplanted cells, and are still experimental. Defects and limitations, including pericapsular fibrotic overgrowth, insufficient oxygen and nutrient diffusion, and device failure, have been reported, and require technological improvements before the wide clinical use.

One of the greatest potential theoretical concerns with pluripotent stem-cell–derived therapies is the risk for tumorigenicity. ESCs and iPSCs both have the ability to proliferate indefinitely; and the degree of purity of the final product or the lack of complete differentiation can result in the retention of undifferentiated cells which can give rise to teratomas (Zhang & Li, 2020). Other risks are genomic and epigenetic instability over prolonged culture, contamination with unwanted cell types. To date there are no reports of malignant transformation in human diabetes trials with follow-up up to 5 years of treatment, but the number of patients treated is still small and the observation period is still short to rule out rare late events. Even a small number of undifferentiated cells has the potential to initiate tumor growth in permissive conditions, as shown by preclinical models, and this highlights the importance of having sound purification protocols, and well-established potency assays and standardized genomic stability testing before bringing them into clinical use.

Other safety concerns include manufacturing consistency and quality control. Stem-cell therapies require several complex procedures, such as screening potential donors, isolating cells, expanding or differentiating them in the lab and storing them. Any of these steps can contribute to variability in potency, immunogenicity and safety. The lack of consistency with Good Manufacturing Practice (GMP) standards can lead to microbial contamination, exposure to endotoxins and batch-to-batch variability (Doe et al., 2025). Another challenge is the absence of uniformly agreed upon release criteria, which means that patients in other trials are likely to be receiving different products labeled “MSC” or “iPSC-derived β-like cells.” Especially the reporting of manufacturing procedures, cell characterization and quality control assays will be essential for making the results reproducible and comparable between studies.

The most unanswered questions may relate to the safety of stem-cell–based interventions over a long period of time. Durability of metabolic benefit and/or late onset complications like chronic graft dysfunction, immune relapse or malignant transformation have not been assessed in most published trials, as follow up periods were short, up to 9—12 months (El-Badawy et al., 2016; Koishybayeva et al., 2025). Others have found that patients who became insulin independent in the short term subsequently went into insulin dependence again within 1-2 years, indicating that long-term functional persistence of transplanted or stimulated β-cells is limited. Hence it is essential to have long-term monitoring systems in place. Follow up should involve an HbA1C and stimulated C-peptide assessment at least every 3-6 months for the first year and then annually. Adverse event surveillance should be systematic and include immune complications, graft viability and potential tumorigenesis. For high-risk populations, there should be further monitoring with imaging or biomarker-based approaches with pluripotent stem-cell–derived products.

Late onset adverse events may be rare, and could only be identified with large populations, so multicenter registries are essential. International partnerships will be required to set up registries which

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will be able to measure safety and efficacy results for 5-10+ years after treatment. These should collect the standardised data of graft function, adverse events and clinical outcomes, and promote the sharing of positive and negative results. This would reduce publication bias and more closely represent the long-term risk benefit profiles.

To summarize, while stem-cell therapies for diabetes, especially MSCs, appear to be relatively safe in the short term, the long-term safety of these treatments has not been established. Immunosuppression, conditioning regimens, tumorigenicity and manufacturing variability are potential risks that need to be addressed by robust clinical protocols, open reporting and additional surveillance. Achieving GMP compliant production standards, implementing international safety registries and ensuring regular long-term monitoring will be critical to ensure the safe development of stem-cell therapies for diabetes and ensure they offer patient benefit.

Regulatory and practical recommendations

Below are clear, actionable regulatory and practical recommendations to help move stem-cell therapies for diabetes from experimental studies toward safe, reproducible clinical use. Treat this as a submission-ready checklist you can include in the manuscript or give to trial teams and regulators.

1. Early regulatory engagement: Engage regulators early and often. Before first-in-human work, pursue pre-IND (or equivalent) meetings with relevant authorities to agree on safety requirements, nonclinical packages, and initial clinical endpoints. Alignment up front shortens review cycles and reduces the risk of later trial hold or redesign.

2. Follow Good Manufacturing Practice and transparent product characterization: Produce all cell products in GMP-certified facilities. Document and publish manufacturing protocols, donor screening criteria, passage number limits, culture media components, release criteria, sterility testing, mycoplasma and endotoxin limits, and cryopreservation methods. Include validated potency assays that correlate with intended mechanism (for example, insulin secretion for β-cell products or defined immunomodulatory markers for MSCs).

3. Standardize product identity and release criteria: Define and report a minimal set of characterization metrics for each product: phenotype markers (flow cytometry), viability, purity (residual undifferentiated cells), functional assays (glucose-stimulated insulin secretion or immunomodulatory assays), genomic stability testing, and batch potency. Use these criteria as mandatory release tests and report them in trial manuscripts.

4. Harmonize clinical endpoints and definitions: Adopt standardized efficacy and safety endpoints across studies to allow comparison and pooling. Recommended primary/secondary measures: stimulated C-peptide (mixed-meal tolerance test) at 12 months, change in HbA1c, time to insulin independence (with a clear, prespecified definition), daily insulin dose, and patient-reported outcomes. Predefine adverse event categories and grading (use CTCAE where appropriate).

5. Risk mitigation and trial design: Use staged dose escalation and sentinel dosing for novel products. For pluripotent-derived implants require evidence of minimal residual undifferentiated cells and consider local safety measures (encapsulation, retrieval strategy). For trials involving conditioning or immunosuppression, provide detailed infectious disease prophylaxis and monitoring plans. Wherever feasible, use randomized controlled designs or well-matched comparators to reduce bias.

6. Informed consent and patient selection: Provide explicit, plain-language consent documents that describe known risks, uncertainty about long-term harms, likelihood of benefit, and alternative treatments. Limit early trials to centers with appropriate critical care and expertise. Use clear inclusion/exclusion criteria to protect participants at elevated risk of complications.

7. Long-term surveillance and registries: Mandate entry into an independent registry for all trial participants and treated patients, with minimum follow-up of five to ten years. Capture standardized safety signals (malignancy, graft failure, immune events), metabolic outcomes, and device-related complications when applicable. Make de-identified registry data available for pooled analyses.
8. Adverse event reporting and stop criteria: Define clear, prospectively specified stopping rules for unexpected severe adverse events. Commit to rapid reporting of suspected unexpected serious adverse reactions (SUSARs) to regulators and ethics committees. Share serious safety signals publicly and publish negative or null results to prevent publication bias.
9. Quality assurance, audits, and traceability: Implement batch traceability, unique product identifiers, cold chain logs, and audit trails. Allow independent audits by regulators or accredited third parties. Maintain donor and product traceability for the lifespan of the registry follow-up period.
10. Data standards, sharing, and transparency: Preregister protocols and statistical analysis plans. Use common data elements and adopt data standards to facilitate meta-analysis. Commit to timely sharing of de-identified trial datasets, safety reports, and manufacturing protocols (redacting proprietary details only when necessary).
11. Post-marketing and conditional approval pathways: If early trials show promise, pursue conditional or accelerated approval with strict post-marketing commitments: mandatory registry enrollment, predefined confirmatory trials, and periodic re-assessment of risk-benefit as long-term data mature.
12. International harmonization and ethical oversight: Coordinate with international consortia to harmonize standards, especially for cell sourcing, cross-border tissue transfer, and ethics approvals. Ensure independent ethical oversight, and involve patient representatives in governance of registries and trial design.

Future Directions

Stem-cell therapy for diabetes is in an era of proof-of-concept, but definitive proof is yet to be generated. There are a number of key points that need to be considered if experimental interventions are to be translated into routine therapeutic options. Future studies should break away from the small, single-center pilot studies and embrace large, multicenter, randomized controlled designs, first. These trials are important to address variability, minimize bias, and ensure the results are sufficiently powered to determine efficacy and safety. Standardized outcome variables such as stimulated C-peptide response, HbA1c change, insulin dose reduction, and definition of insulin independence should be uniformly used to compare between studies and to allow a good meta-analysis to be performed.

Second, the sustainability of the treatment effects should be better understood. Many patients relapse within one to two years after stem-cell therapy, but some become insulin independent or can cut back on exogenous insulin. Further trials are necessary to determine if repeated doses, immunomodulation or combination therapy is necessary to maintain benefits. Likewise, long-term monitoring is essential to assess for any long term risks such as graft failure, chronic immune rejection or malignant transformation. Real world safety data will require international registries with 5-10 years of follow-up.

Thirdly, there is a need to enhance manufacturing and delivery platforms to guarantee reproducibility and risk reduction. Well defined and standardized cell products will be a critical requirement of GMP production. New developments in encapsulation technologies could boost graft survival and limit the use of systemic immunosuppression, and a new genetic engineering technique, such as CRISPR-mediated modification of graft cells, could increase the safety and effectiveness of cell transplants. The

combined use of these bioengineering techniques and stem-cell therapy could enhance the effectiveness of the approach, while reducing the risks.

Fourth, improved methods of patient selection are needed. Newly diagnosed or those with preserved β-cell function seem to be more responsive to some stem-cell modalities. Stratified trial designs taking account of disease stage, immune status, and disease comorbidities can provide more precise clinical recommendations and optimize outcomes.

Last but not least, ethical and legal standards need to keep pace with this scientific development. Clear and open disclosure of the trial design, production, and side effects will be crucial to ensure public confidence. Rigorous and responsible testing of promising therapies should be ensured through clear regulatory pathways, with a focus on preventing the commercialization of unproven therapies and interventions. There will also be a strong focus on engaging patients and advocacy groups to ensure that research priorities are relevant to patients' needs and perspectives.

Overall, future studies should concentrate on large scale, well-designed trials, extended surveillance, standardized manufacturing and endpoints, incorporation of bioengineering strategies and strong ethical and regulatory oversight. Solving these priorities is the key to whether stem-cell therapies can live up to their promise of being a safe, effective treatment for diabetes.

Conclusion

The future of stem cell therapies in the therapy of diabetes is an exciting prospect that brings along two approaches, immune modulation and β-cell replacement. The preliminary clinical studies of MSCs, HSCs, ESCs, and iPSCs have shown modest improvements in glycemic control, the recovery of β-cell function, and even temporary insulin independence in a subset of patients. However, available evidence is small, short follow-up, variable manufacturing and endpoints are quite heterogeneous. Safety issues such as tumorigenicity and theoretical tumorigenicity as well as risks associated with immunosuppression and conditioning regimes, continue to be the biggest hurdles for widespread use.

Progress in the future will rely on the conduct of large multicenter controlled randomized trials with consistent efficacy and safety endpoints, including stimulated c-peptide, HbA1c, insulin requirements and uniformly established criteria for insulin independence. Rare or delayed complications will also require long-term surveillance frameworks and international registries to properly capture them, and a monitoring of metabolic benefits' durability will be essential. But also the creation of GMP processes, potency assays validated and reporting product characterization and quality control will be critical. However, with the development of new technologies, such as encapsulation, gene editing, and other bioengineering methods, the safety and effectiveness of these treatments could be further improved. Last, there is a need for ethical and regulatory oversight of the translation process to ensure that it is carried out in a responsible manner, and that unproven interventions are not prematurely used in clinical practice. To sum up, the stem-cell therapy for diabetes is not just a theory anymore but is still in the experimentation stage. These interventions can be developed into safe and effective treatments with rigorous clinical evaluation, uniform methodologies and with long-term monitoring.These interventions can be transformed into safe and effective treatments that could change the way diabetes is managed, with rigorous clinical evaluation, standardized methodologies and sustained long-term monitoring.

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