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MINIREVIEWS

Stem cell therapy for diabetes: Advances, prospects, and challenges

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Abstract

Diabetes mellitus, a global epidemic, represents a major public health threat. Stem cell therapy, with its regenerative capacity, has emerged as a promising approach for diabetes mellitus management. This paper reviews recent advancements, prospects, and challenges in stem cell-based treatments for diabetes mellitus, focusing on the applications of induced pluripotent stem cells and mesenchymal stem cells, the development of pancreatic islet organoids, and the potential for personalized medicine. The review critically assesses the efficacy and safety of stem cell therapies in clinical trials and examines their applications in both type 1 and type 2 diabetes mellitus. Despite the promising potential, challenges such as safety concerns, transplantation efficiency, ethical considerations, and immune rejection remain prevalent. Lastly, the paper discusses future directions, including the integration of stem cell therapy with other treatments and the advancement of personalized therapeutic strategies, offering new perspectives and hope for diabetes mellitus management.

Key Words: Diabetes mellitus; Stem cell therapy; Induced pluripotent stem cells; Mesenchymal stem cells; Clinical applications

Core Tip: Stem cell therapy emerges as a transformative approach, leveraging dual mechanisms: Differentiation into glucose-responsive β-cells and immunomodulation *via* paracrine signaling. Recent advancements include vertex pharmaceuticals' VX-880 trial, where patients demonstrated restored insulin production and a significant reduction in exogenous insulin dependence. Challenges such as tumorigenicity in pluripotent stem cells and immune rejection are addressed through clustered regularly interspaced short palindromic repeats-edited human leukocyte antigen knockouts and encapsulation technologies. Innovations like three dimensional-bioprinted organoids and artificial intelligence-driven personalized regimens integrating MSC-pharmacotherapy synergies exemplify the next frontier, promising scalable, precision solutions to redefine diabetes management and mitigate complications.

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INTRODUCTION

Diabetes mellitus has reached pandemic proportions, with global prevalence doubling from 7% to 14% among adults between 1990 and 2022, now affecting 830 million individuals worldwide[1]. Conventional therapies, including metformin, sulfonylureas, and insulin injections, remain the standard of care[2,3]. However, they primarily alleviate symptoms rather than address the disease's fundamental pathophysiology irreversible pancreatic β-cell loss and systemic insulin resistance[4]. These treatments, through drug-mediated glucose regulation and exogenous insulin supplementation, do not restore endogenous β-cell function nor prevent disease progression, leaving patients susceptible to debilitating complications such as retinopathy, nephropathy, and cardiovascular diseases.

Stem cell therapy offers a paradigm shift by targeting these unmet needs through two complementary mechanisms: (1) Direct differentiation into glucose-responsive β-cells to replenish damaged islets[5]; and (2) Immunomodulation *via* paracrine signaling to suppress autoimmune destruction in type 1 diabetes mellitus (T1DM) and mitigate chronic inflammation in type 2 diabetes mellitus (T2DM)[6,7]. This dual capacity regenerative potential combined with microenvironmental remodeling positions stem cells as a transformative approach for achieving sustained glycemic control and halting diabetic complications.

This review critically examines recent advances in stem cell-based therapies, focusing on clinically relevant strategies using induced pluripotent stem cells (iPSCs), mesenchymal stem cells (MSCs), and bioengineered islet organoids. It also addresses ongoing challenges related to safety (tumorigenicity, immunogenicity), efficacy (cell survival, engraftment), and translational barriers (ethical and regulatory considerations), proposing integrative solutions such as combinatory therapies and artificial intelligence (AI)-driven personalized approaches. By bridging preclinical findings with clinical trial outcomes, this review aims to facilitate the transition from experimental models to practical applications in diabetes mellitus care.

PRINCIPLES AND MECHANISMS OF STEM CELL THERAPY FOR DIABETES MELLITUS

Diabetes mellitus comprises two distinct clinical entities: T1DM, characterized by autoimmune-mediated β-cell destruction, and T2DM, driven by insulin resistance and progressive β-cell dysfunction[8,9]. Stem cell therapies target these divergent pathologies through three interconnected mechanisms: (1) Direct differentiation into insulin-producing β-cells; (2) Paracrine-mediated regeneration of endogenous islets; and (3) Immunomodulation to counteract autoimmune or inflammatory damage[10] (Figure 1).

Stem cell differentiation into pancreatic β-cells

Stem cells exhibit multi-directional differentiation potential, enabling them to transform into pancreatic β-cells under specific induction conditions. *In vitro*, both embryonic stem cells (ESCs) and iPSCs can be stepwise induced through agents such as activin A, *FGF10*, insulin-like growth factor-1 (IGF-1), and nicotinamide, progressing from ESC/iPSC to endoderm cells, pancreatic progenitor cells, endocrine progenitor cells, and mature pancreatic β-cells[11]. These differentiated β-cells closely resemble their natural counterparts in both structure and function, responding to fluctuations in blood glucose and secreting appropriate insulin amounts to regulate glucose homeostasis[12].

Paracrine-mediated islet regeneration

Stem cells, particularly MSCs, secrete a range of cytokines and growth factors, including IGF-1, hepatocyte growth factor (HGF), and vascular endothelial growth factor (VEGF). (1) IGF-1 activates phosphatidylinositol 3-kinase (PI3K) and protein kinase B (AKT) signaling, inhibiting β-cell apoptosis and enhancing glucose-stimulated insulin secretion[13,14]; (2) HGF promotes β-cell proliferation through c-Met receptor activation, increasing islet mass in T2DM models[15]; and (3) VEGF induces neoangiogenesis, improving islet perfusion and oxygen/nutrient supply, preventing hypoxia-induced

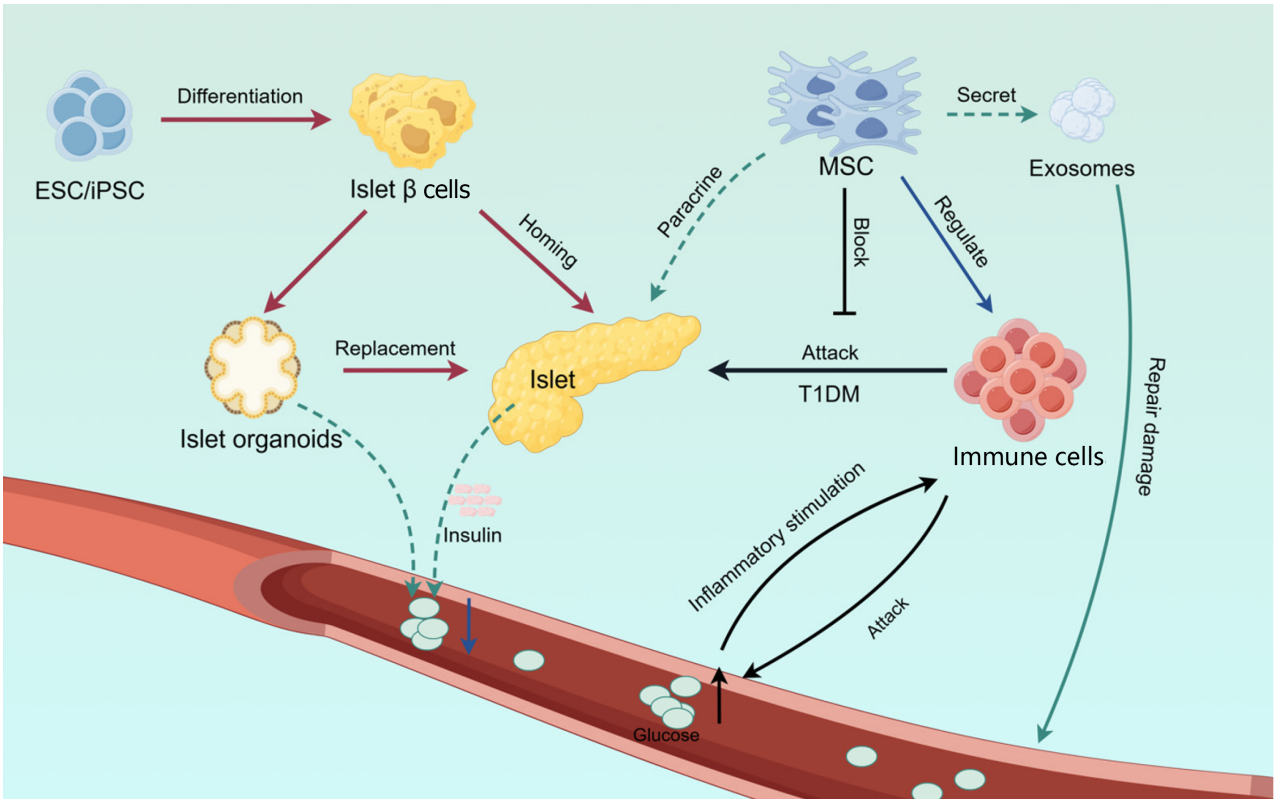

Figure 1 Mechanisms of stem cell therapy for diabetes mellitus. This figure outlines the mechanisms by which stem cell therapy addresses diabetes. It includes the differentiation of stem cells into insulin-producing β-cells, paracrine effects that promote β-cell regeneration, and immunomodulation that reduces autoimmune damage and inflammation. Collectively, these processes enhance glucose regulation and facilitate pancreatic repair. ESC: Embryonic stem cells; iPSC: Induced pluripotent stem cells; MSC: Mesenchymal stem cell; T1DM: Type 1 diabetes mellitus.

β-cell loss[16]. Transplantation of MSCs into diabetic rat models has been shown to stimulate pancreatic β-cell proliferation, enhance insulin secretion, and reduce blood glucose levels.

Immunomodulation in diabetes mellitus pathogenesis

In T1DM, an autoimmune condition in which the immune system attacks pancreatic β-cells, MSCs possess immunomodulatory properties that can curb excessive immune activation, reduce autoimmune responses against β-cells, and inhibit T lymphocyte proliferation and activation. By modulating the Th1/Th2 balance, MSCs decrease Th1 cytokine secretion (*e.g.*, interferon-γ and tumor necrosis factor-α) and increase Th2 cytokine secretion (*e.g.*, interleukin-4 and interleukin-10), mitigating inflammation and immune-mediated damage[17]. Additionally, MSCs can promote the generation of regulatory T cells, which exert immunosuppressive functions, safeguarding β-cells from autoimmune attack[18,19]. Clinical studies have demonstrated that patients with T1DM receiving MSC therapy exhibit reduced autoantibody levels, diminished immune cell activation, enhanced pancreatic β-cell function, and improved glucose control[20,21].

APPLICATION OF STEM CELL THERAPY IN THE TREATMENT OF DIABETES MELLITUS

Application of ESCs and iPSCs in diabetes mellitus treatment

ESCs and iPSCs, with their remarkable self-renewal capacity and multilineage differentiation potential, have become critical tools in advancing diabetes mellitus therapeutics. A pivotal moment in this field occurred in 2006 when D'Amour *et al*[22] developed a five-step differentiation protocol to convert human ESCs into functional insulin-secreting cells capable of producing various pancreatic hormones[22], including insulin, glucagon, somatostatin, pancreatic polypeptide, and growth hormone-releasing peptide. *In vivo* studies subsequently demonstrated that these cells could alleviate hyperglycemia in diabetic mouse models, marking the beginning of stem cell-based interventions in diabetes mellitus treatment.

Recent breakthroughs further highlight the transformative role of ESCs and iPSCs in treating both T1DM and T2DM. For T1DM, the primary therapeutic approach focuses on differentiating ESCs/iPSCs into functional pancreatic β-cells to restore lost islet populations and endogenous insulin secretion. A landmark clinical trial by vertex pharmaceuticals (VX-880) showcased remarkable efficacy: 90 days after a single dose of stem cell-derived islet cells, patients exhibited restored insulin production and a 91% reduction in dependence on exogenous insulin[23]. Extended phase 1/2 trial data (NCT04786262) further substantiated these results, with 12 patients with T1DM achieving glucose-responsive insulin secretion following full-dose VX-880 infusion, and 11 participants reducing or eliminating insulin injections by 2024.

Concurrently, in China, the Peking University Stem Cell Research Center and Tianjin First Central Hospital pioneered the first chemically reprogrammed iPSC-derived islet transplantation for T1DM in 2023 (ChiCTR2300072200). The recipient achieved physiological glycemic regulation within 75 days and maintained insulin independence for over a year, marking a significant milestone toward a functional cure for T1DM[24].

In T2DM, ESC/iPSC-based therapies address two key mechanisms: Reducing insulin resistance and promoting β-cell regeneration. A groundbreaking study led by Cheng X's team (Chinese Academy of Sciences' Center for Excellence in Molecular Cell Science) and Yin H's group (Shanghai Changzheng Hospital) exemplifies this strategy[25]. By transplanting autologous iPSC-derived regenerative islet tissue (E-islets) into a T2DM individual with pancreatic injury, they achieved sustained glycemic control, reduced reliance on exogenous insulin, and observed no tumorigenic or immunological complications, as reported in Cell Discovery (2024)[25]. These findings underscore the versatility of stem cell platforms in addressing diverse diabetic pathologies.

Application of MSCs in diabetes mellitus treatment

MSCs, multipotent stromal cells found in adult tissues such as bone marrow, adipose tissue, umbilical cord, and placenta, have gained significant attention in diabetes mellitus therapeutics due to their low immunogenicity and potent immunoregulatory properties. Current clinical trial registries (ClinicalTrials.gov) indicate that 63.6% (77/121) of diabetes mellitus-related stem cell interventions utilize MSCs, with umbilical cord-derived MSCs being the most common source (38 studies), followed by bone marrow (16 studies) and adipose tissue (13 studies) (Table 1). In addition to glycemic control, MSC-based therapies have shown significant efficacy in treating diabetic complications, including nephropathy, myopathy, and chronic foot ulcers.

Recent research highlights that the therapeutic effects of MSCs are largely attributed to their strong immunomodulatory functions and paracrine signaling capabilities. By migrating to damaged tissues, MSCs secrete bioactive substances, such as exosomes, VEGF, and HGF, while modulating the expression of inflammatory cytokines like interleukin-6 and tumor necrosis factor-α, thereby fostering a microenvironment conducive to tissue repair[26,27]. Although the precise mechanisms in T2DM are still under investigation, clinical evidence supports their effectiveness in both T1DM and T2DM. A meta-analysis of 13 studies involving 302 patients found that MSC treatment improved blood glucose regulation, with insulin requirements decreasing from approximately 0.6 to 0.4 units, and a significant reduction in glycated hemoglobin[28]. Another meta-analysis focused on diabetic foot ulcers demonstrated that stem cells were far more effective than conventional treatments, significantly improving patients' quality of life. The stem cell-treated group showed higher ulcer and wound healing rates (201/263 cases *vs* 92/270 in the control group) and a significantly greater rate of neovascularization (49/92 cases *vs* 7/111 cases in the control group). Additionally, the amputation rate was markedly lower in the stem cell-treated group compared to the control group (13/184 cases *vs* 63/227 cases)[29].

Mechanistic insights and early clinical evidence

Pioneering studies in 2006 revealed that MSCs exhibited tropism toward pancreatic islets and glomeruli in diabetic mice, initiating tissue repair processes[30]. Further research demonstrated that MSC-derived interleukin-1Ra inhibits interleukin-1 pathway activation, reversing β-cell dedifferentiation and restoring islet function in T2DM models[31]. Additional work by Khatri *et al*'s team confirmed MSC-mediated pancreatic regeneration in streptozotocin-challenged models, where intrapancreatic MSC administration mitigated β-cell destruction[32].

Combatting diabetic complications

Vascular pathologies: Chronic hyperglycemia-induced inflammation (tumor necrosis factor-α, interleukin-6) and oxidative stress are key drivers of both macrovascular (*e.g.*, atherosclerosis) and microvascular (*e.g.*, nephropathy) complications. A 2024 multicenter trial (NCT01719640) involving 97 patients with T2DM demonstrated that combined bone marrow MSC/mononuclear cell therapy resulted in a 50.6% increase in C-peptide levels. An 8-year follow-up revealed significantly reduced macrovascular (13.8% *vs* 44.8% in the control group) and neuropathic complications (10.3% *vs* 48.3% in the control group)[33-35].

Diabetic foot ulcers: MSC administration, whether *via* local injection or intravascular delivery, enhances wound healing by activating PI3K/AKT and mitogen-activated protein kinase/extracellular regulated protein kinases (ERK) pathways, promoting epithelialization and angiogenesis. A cohort study involving five groups with 216 participants confirmed the efficacy of MSCs in promoting ulcer healing. The bone marrow-MSC group achieved 100% ulcer healing significantly faster than the bone marrow-mononuclear cells group within 6 weeks following cell therapy. Additionally, bone marrow-MSC therapy demonstrated superior safety and tolerance, as well as enhanced efficacy in improving lower limb perfusion and foot ulcer healing in diabetic patients with severe limb ischemia, compared to bone marrow-mononuclear cells therapy. Data indicate that MSCs derived from bone marrow and adipose tissue achieved an 88% success rate in treating diabetic foot ulcers, highlighting the safety and effectiveness of MSC transplantation in preventing limb amputations[36, 37].

Diabetic nephropathy: Six registered clinical trials investigate the use of MSCs in treating renal complications. MSCs mitigate renal fibrosis through Smad2/3 pathway inhibition and by secreting VEGF/HGF, which improves microcirculation. Their anti-inflammatory action includes downregulation of monocyte chemoattractant protein-1 and M2 macrophage polarization, leading to a reduction in interleukin-1β/interleukin-6/tumor necrosis factor-α levels[38-40]. Additionally, exosome-mediated modulation of the extracellular matrix further delays the progression of fibrosis[41,42]. A 2024 case report from Pakistan American Hospital documented the successful improvement of a patient's renal condition using umbilical cord-derived Wharton's jelly MSCs and exosomes, further supporting the clinical translatability of

Table 1 Clinical trials of mesenchymal stem cell-based stem cell therapies for diabetes

MSCs source	Clinical trials					
	Diabetes	Type 1 diabetes	Type 2 diabetes	Diabetic foot	Diabetic nephropathy	Others
Umbilical cord-derived MSCs	NCT04972890 NCT05631444 NCT06751199 NCT02579148	NCT01143168 NCT01219465 NCT01374854 NCT03484741 NCT05003908 NCT06407297	NCT01142050 NCT01413035 NCT01954147 NCT02302599 NCT02886884 NCT02945449 NCT03751735 NCT04441658 NCT04501341 NCT05507697 NCT06727721	NCT02672280 NCT06373809 NCT01216865 NCT02834858 NCT04104451 NCT04464213 NCT06231771 NCT06812637	NCT03288571 NCT04125329 NCT04562025 NCT04216849	NCT02745808 NCT02763423
Bone marrow-derived MSCs	NCT02387749	NCT01157403 NCT03361631 NCT02893306 NCT04078308	NCT00644241 NCT01694173 NCT01719640 NCT01759823 NCT03343782 NCT03943940	NCT01686139 NCT00955669 NCT02796079 NCT03248466 NCT05783115		
Adipose-derived MSCs	NCT01257776	NCT02940418 NCT03920397 NCT05308836	NCT06605508	NCT03259217 NCT05610865 NCT03865394 NCT03916211 NCT04466007 NCT05595681	NCT04869761 NCT03840343	
MSCs from other sources	NCT02384018	NCT01496339		NCT06003530		
Unknown origin MSCs	NCT04776239	NCT00646724 NCT01068951 NCT02057211 NCT04061746 NCT01322789	NCT01786707 NCT02286128	NCT02304588		

MSC: Mesenchymal stem cell.

this approach[43].

Application of stem cell-derived exosomes in diabetes mellitus

Stem cell-derived exosomes, a subset of extracellular vesicles (30 nm-150 nm in diameter) enclosed by lipid bilayers, have emerged as a promising cell-free therapeutic strategy for diabetes mellitus and its complications. These nanoscale particles retain the reparative properties of their parental MSCs while bypassing immunogenicity concerns due to the absence of intact cellular components. Their cargo, which includes proteins, lipids, and regulatory RNAs, allows for precise modulation of target cell activity through membrane fusion or endocytosis[44]. This combination of biocompatibility and functional versatility positions exosomes as effective mediators in diabetic wound healing, retinopathy management, and metabolic regulation.

In diabetic wound repair, exosomes counteract hyperglycemia-induced impairments through multiple mechanisms. Local administration of placental MSC-derived exosomes accelerates wound closure by enriching miR-145-5p, which suppresses cyclin-dependent kinase inhibitor 1A, activating Erk/Akt signaling pathways to enhance fibroblast proliferation, migration, and apoptosis resistance[45]. Additionally, exosome-mediated adenosine 5′-monophosphate-activated protein kinase /*ULK1* autophagy induction alleviates muscle atrophy, while the coordinated suppression of oxidative stress and inflammation, in combination with angiogenesis and collagen remodeling, helps restore tissue integrity[46,47]. Preclinical studies further highlight reduced scar width and accelerated epithelial regeneration in animal models, supporting their translational potential.

Exosome therapy also holds promise for diabetic retinopathy, where MSC-derived small extracellular vesicles (MSC-sEVs) mitigate retinal neurodegeneration and pathological angiogenesis. Under hyperglycemic conditions, hypoxia inducible factor (HIF)-1α stabilization inhibits *EZH2* degradation, leading to peroxisome proliferator-activated receptor-gamma coactivator (PGC)-1α suppression *via* methylation, which worsens retinal dysfunction. MSC-sEVs counteract this cascade by delivering miR-5068 and miR-10228, which disrupt the HIF-1α/*EZH2*/PGC-1α signaling pathway. Intravitreal injection of MSC-sEVs in db/db mice and streptozotocin-induced diabetic rats restores retinal function, reduces apoptosis, and alleviates inflammatory infiltration and abnormal neovascularization[48].

Despite these advances, the clinical translation of exosome therapies faces several challenges. First, the standardization and quality control of exosome production remain imperfect, which could affect the stability and reproducibility of their efficacy[49]. Second, the short *in vivo* stability and half-life of exosomes may limit their long-term effectiveness[50]. Furthermore, while exosomes generally exhibit low immunogenicity, their long-term safety and potential immune response risks remain uncertain due to the complexity of clinical applications and individual variability. Therefore,

comprehensive, large-scale, multi-center, long-term clinical trials are essential to assess and verify the safety and efficacy of exosome-based therapies in clinical practice.

CHALLENGES IN STEM CELL THERAPY FOR DIABETES MELLITUS

Safety issues

Despite the transformative potential of stem cell therapy in diabetes mellitus management, safety concerns especially tumorigenicity and immunogenicity remain significant barriers to clinical implementation. PSCs, including ESCs and iPSCs, inherently pose oncogenic risks due to their unchecked proliferative capacity. Transplanting insufficiently differentiated ESCs or iPSCs increases the likelihood of tumor formation[51]. To mitigate these risks, multi-faceted strategies are necessary, including clustered regularly interspaced short palindromic repeats (CRISPR)-mediated knockout of oncogenes (*e.g.*, *MYC*), optimized reprogramming techniques to minimize epigenetic alterations, and rigorous post-transplant monitoring through circulating tumor DNA assays[52-54]. In contrast, clinical data from 62 studies involving 3546 patients indicate that mesoderm-derived MSCs do not exhibit significant adverse reactions during treatment[55]. Only a few patients experienced mild side effects, such as fever and constipation, suggesting that MSCs present a relatively low tumorigenic risk in clinical applications.

Immunogenicity presents another challenge. Allogeneic ESCs, carrying foreign human leukocyte antigen (HLA) haplotypes, trigger robust host immune rejection, while autologous iPSCs although theoretically immune-compatible may acquire immunogenic neo-antigens during reprogramming due to dysregulated gene expression (*e.g.*, aberrant activation of endogenous retroviruses)[56]. MSCs, however, display inherent immune privilege through low major histocompatibility complex (MHC)-II expression, though their immunogenicity can increase with prolonged *in vitro* passaging or exposure to inflammatory cytokines (*e.g.*, interferon-γ), as evidenced by the upregulation of MHC levels in bone marrow-derived MSCs under pro-inflammatory conditions. Moreover, source-dependent variability exists: Umbilical cord MSCs maintain stable low immunogenicity across passages, while adipose-derived and bone marrow-derived MSCs may exhibit higher immunogenicity[57-60].

Current strategies to overcome immune rejection present practical limitations. Autologous iPSC-derived islet transplantation, while avoiding HLA mismatch, is cost-prohibitive and technically complex, restricting its scalability[61]. Allogeneic approaches, such as VX-880, combine HLA-matched donor cells with immunosuppressants (*e.g.*, tacrolimus/mammalian target of rapamycin inhibitors), but long-term immunosuppression raises infection risks and exacerbates diabetic nephropathy[62-64]. Emerging solutions involve CRISPR-based engineering to delete immunogenic loci (*e.g.*, B2M knockout) and introduce immune checkpoint regulators (*e.g.*, programmed cell death ligand 1 overexpression), which could protect MSC-derived islet β-cells from graft rejection in diabetes mellitus treatment without the need for adjunctive immunosuppression[65,66]. Encapsulation technologies, like Vertex's VX-264 (NCT05791201), provide physical immunoisolation for transplanted islet cells, though this approach prioritizes insulin secretion over the intrinsic regenerative functions of stem cells a trade-off that may limit efficacy, particularly in treating T2DM and microvascular complications.

Efficacy challenges

The clinical efficacy of stem cell therapy in diabetes mellitus is contingent upon three interdependent factors: Post-transplantation cell survival, homing efficiency to target tissues, and the functional potency of engrafted cells. Upon administration, exogenous stem cells whether insulin-producing β-cell progenitors or immunomodulatory MSCs are immediately subjected to immune surveillance. Research indicates that a significant proportion of MSCs perish within one day of transplantation in mice, with the surviving cells almost entirely disappearing within 11 days[67]. This attrition is further aggravated by metabolic stressors: Hyperoxic *in vitro* culture conditions predispose cells to oxidative damage, while hypoxic diabetic microenvironments trigger mitochondrial dysfunction and caspase-3 activation[68]. Strategies to enhance cell survival include CRISPR-mediated overexpression of anti-apoptotic genes, such as *Bcl2*[69-71], and autologous cell sourcing to reduce immune recognition.

The homing efficiency of stem cells relies on precise interactions with damaged tissues through various cytokines and signaling pathways. Suboptimal homing efficiency limits the therapeutic potential of stem cells in diabetes mellitus treatment. Currently, the mechanisms governing stem cell homing remain incompletely understood, hindering the accurate targeting of the pancreas and injured tissues. The expression of chemokines or their receptors can significantly enhance homing efficacy. For instance, overexpression of *CCR2* in MSCs substantially improves their immunomodulatory activity and migratory ability. Intravenously infused MSC-*CCR2* exhibits enhanced homing to the lungs and injured tissues, thereby accelerating tissue repair in diabetic wounds[72,73]. Additionally, the *CCR4* and stromal cell-derived factor-1 (SDF-1) chemokine pairs hold promise for further optimization. In diabetic mice, damaged islet tissues secrete SDF-1, and MSCs expressing *CXCR4* respond to this gradient, migrating toward the damaged islet tissues through cytoskeletal rearrangement and chemotaxis. MSCs expressing *CXCR4*, or local injection of SDF-1, significantly improve the homing efficiency of MSCs to islet tissues[74,75].

Genetic engineering of stem cells offers a promising approach to overcoming their inherent therapeutic limitations. While native MSCs primarily exert paracrine immunomodulation, insulin-secreting variants generated *via PDX1*/*NEUROG3* transduction exhibit physiologic glucose responsiveness in primate models[76,77]. Additionally, overexpression of angiopoietin-1 in MSCs has been shown to significantly enhance the survival of human umbilical vein endothelial cells, promote tubule formation, and activate Akt, thereby driving angiogenesis and accelerating wound healing in diabetic mouse models[78].

However, individual differences play a pivotal role in determining the effectiveness of stem cell therapies. Factors such as age, baseline health status, and genetic background of both stem cell donors and patients can alter the *in vivo* microenvironment, subsequently affecting stem cell survival, differentiation, and functionality[79-81]. For example, elderly patients may provide a suboptimal environment for stem cell survival due to age-related declines in physiological functions, while patients with specific genetic profiles may exhibit varying immune responses to stem cells, resulting in diverse therapeutic outcomes.

Ethical and regulatory challenges

The translation of stem cell therapies into clinical practice is hindered by complex ethical and regulatory challenges, particularly in relation to pluripotent cell sources. Despite its transformative potential in diabetes mellitus treatment, ESC research remains entangled in ethical debates due to the inherent requirement for embryo destruction. Germany's Embryo Protection Act (1991) illustrates stringent regulations prohibiting the derivation of human ESCs, reflecting widespread concerns about the commodification of embryos, a risk that intensifies when using surplus *in vitro* fertilization embryos or tissues derived from abortions for cell line development[82]. This ethical dilemma has prompted a shift toward alternative sources of pluripotent cells, such as iPSCs, which are reprogrammed from somatic cells without involving embryos, thereby sidestepping the moral issues associated with ESC use[83]. In parallel, MSCs, sourced from bone marrow, umbilical cord, or adipose tissue, have gained prominence due to their non-controversial procurement. However, ethical considerations remain regarding donor consent and material traceability. For example, clinical samples, such as bone marrow aspirates, require documented consent for secondary research use, with strict protocols governing the disposal of biological materials at each phase of clinical trials.

Regulatory fragmentation further complicates the development of stem cell-based therapies. As of 2025, only a few countries have implemented dedicated frameworks for stem cell product manufacturing, leading to inconsistent quality control standards for critical processes, such as cryopreservation (-196 °C liquid nitrogen 2 storage) and viral vector testing. A unified and comprehensive quality assessment system is essential to ensure clinical safety. Currently, global regulatory policies for stem cell therapies vary widely, with inconsistent standards posing significant obstacles to the conduct of clinical trials, the approval process, and the commercialization of stem cell-based treatments.

TECHNOLOGICAL BREAKTHROUGHS AND FUTURE DEVELOPMENT PATHWAYS IN STEM CELL THERAPY FOR DIABETES MELLITUS

Technological innovations and breakthroughs in stem cell therapy

Recent advancements in stem cell therapy for diabetes mellitus are fueled by innovations in cell sourcing, genetic engineering, and biohybrid technologies. The discovery of novel stem cell sources, such as amniotic stem cells, presents distinct advantages for clinical translation, owing to their low immunogenicity and cost-effective isolation methods, which significantly reduce the risk of immune rejection[84]. Similarly, urine-derived stem cells offer a non-invasive alternative for autologous therapies, circumventing ethical concerns while retaining differentiation potential[85].

Gene-editing technologies are reshaping therapeutic strategies by enhancing functional precision. Targeted modifications allow for the deletion of tumorigenic genes and the insertion of anti-apoptotic or insulin-secretory pathways, thereby improving both safety profiles and glucose-regulatory efficacy. For example, CRISPR-mediated knockout of HLA class I genes in iPSCs reduces graft rejection, while overexpression of *PDX1* increases β-cell differentiation efficiency[66].

The integration of tissue engineering with stem cell technology provides additional innovative solutions. Techniques such as three-dimensional (3D) printing and microfluidics enable the creation of bio-scaffolds with precise architectures, creating optimal environments for stem cell growth and differentiation. Microfluidic systems allow for precise spatiotemporal control over growth factor gradients (*e.g.*, *Wnt* and *FGF* families), directing stem cells toward glucose-responsive islet organoids that mimic native pancreatic structures[86,87]. Advances in 3D printing have also facilitated the delivery of stem cells encapsulated in hydrogels and other nanomaterials, enhancing transplantation efficiency and cell survival. For instance, dual-network micro-fibrous encapsulation using alginate and hyaluronic acid methacrylate protects pancreatic α-cells and β-cells, preserving their bioactivity and supporting effective nutrient and metabolite exchange[88]. Bioengineered scaffolds also enable localized stem cell delivery: GelMA hydrogels protect adipose-derived stem cells from hyperglycemic stress while promoting angiogenesis in chronic wounds[89,90], while dual-network microfibers sustain β-cell viability through optimized nutrient exchange[91]. Collectively, these innovations represent a multidisciplinary approach to overcoming current challenges related to scalability, efficacy, and safety[92].

Combined treatment strategies

The synergistic integration of stem cell therapy with conventional glucose-lowering medications and immunosuppressive regimens represents a transformative approach to diabetes mellitus management. Combining MSCs with pharmacological agents such as insulin, metformin, or glucagon-like peptide-1 receptor agonists achieves dual therapeutic goals: Rapid glycemic stabilization through drug-mediated metabolic control and long-term β-cell regeneration *via* stem cell-driven restoration and immunomodulation[93]. In T1DM, where extensive β-cell destruction leads to severe insulin deficiency, concurrent stem cell transplantation and insulin therapy offer significant clinical benefits. This strategy reduces exogenous insulin dependence and mitigates adverse effects of intensive insulin regimens, such as hypoglycemia and weight gain. Moreover, combining MSCs with anti-diabetic drugs holds promise for treating complications like diabetic foot ulcers and nephropathy, where stem cells promote tissue repair and pharmacological agents correct systemic

metabolic imbalances.

Immunosuppressant co-administration plays a vital role in optimizing outcomes for β-cell or islet transplantation, particularly in autoimmune-mediated T1DM. While MSCs naturally suppress inflammatory responses through the paracrine secretion of anti-inflammatory cytokines, adjunctive immunosuppressants, such as tacrolimus or mycophenolate mofetil, provide further protection against residual autoimmune attacks on transplanted cells. Clinical evidence indicates that this combinatorial approach significantly enhances graft survival, improves β-cell function, and stabilizes glycemic variability, thereby reducing the incidence of acute metabolic complications.

Personalized treatment strategies

The advent of precision medicine has accelerated the development of patient-tailored stem cell therapies, addressing the inherent variability in treatment responses caused by differences in stem cell sources, culture protocols, and patient profiles. Personalized strategies leverage comprehensive datasets, including genetic predispositions, epigenetic modifications, disease progression markers, and comorbidities to optimize therapeutic precision. AI algorithms analyze these multidimensional datasets to predict individual responses to specific stem cell lineages or differentiation protocols, enabling clinicians to customize interventions based on factors like age, sex, disease severity, and complication profiles. For example, machine learning models trained on longitudinal clinical data can identify optimal timing and dosage regimens for MSC administration, maximizing engraftment efficiency while minimizing off-target effects.

Advances in gene-editing technologies further refine personalized approaches by correcting diabetes mellitus-associated genetic mutations (*e.g.*, monogenic defects in maturity-onset diabetes of the young subtypes) or engineering stem cells to express patient-specific immune tolerance markers. Simultaneously, bioinformatics tools elucidate the molecular pathways underlying stem cell-mediated β-cell regeneration, enabling the selection of targeted therapeutic modalities. AI-driven predictive analytics also enhance risk stratification by integrating real-time continuous glucose monitoring data with histocompatibility profiles, facilitating preemptive adjustments to treatment plans. This shift towards individualized therapy not only improves clinical outcomes but also streamlines healthcare resource allocation by reducing trial-and-error inefficiencies.

CONCLUSION

Stem cell-based therapies have the potential to transform diabetes mellitus management through mechanisms such as β-cell differentiation, endogenous regeneration, and immunomodulation. Although preclinical studies and early-phase clinical trials yield promising results, progress toward clinical implementation is still hindered by challenges, including tumorigenicity risks, variable therapeutic efficacy, immune rejection, and evolving regulatory frameworks. Overcoming these challenges will require innovations in cell engineering, biomaterial science, and quality control protocols. Emerging technologies, such as CRISPR-based gene editing, 3D-bioprinted tissue constructs, and AI-optimized combinatorial regimens, are well-positioned to address current obstacles, paving the way for standardized, scalable therapeutic platforms. As research deepens our understanding of stem cell biology and patient-specific disease mechanisms, these therapies are expected to transition from experimental approaches to mainstream clinical solutions, providing durable, precision-targeted strategies for managing diabetes mellitus and its complications.

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FOOTNOTES

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