

REVIEWS

Beyond Efficacy: How Extraction Location and Other Considerations Affect the Future of Diabetes Stem Cell Therapy

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This narrative review evaluates the potential of stem cell–based therapies in curing the underlying causes of diabetes type 1 and type 2, with a focus on the accessibility, safety, and efficacy of various stem cell extraction locations compared with standard diabetes treatments. We identified studies examining various stem cell types and sources, including embryonic stem cells, bone marrow–derived hematopoietic stem cells, neural stem cells, umbilical cord–derived mesenchymal stem cells, and adipose-derived stem cells. Among these, umbilical cord and adipose stem cells appear to offer the strongest potential for treatment, with both lasting results and easy accessibility. However, barriers such as cost, feasibility, and the durability of long-term outcomes must still be considered. While stem cell therapies offer an exciting avenue for the treatment of diabetes, further research is necessary to resolve these challenges and position stem cell transplant as a viable alternative to existing therapies, including exogenous insulin and oral hypoglycemic medications.

Introduction

Diabetes is a group of metabolic diseases characterized by hyperglycemia due to insufficient secretion of insulin (type 1) or insulin resistance (type 2).¹ In type 1 diabetes (T1D), insulin-producing pancreatic β -cells are destroyed following an autoimmune attack, requiring these patients to administer daily insulin injections. C-peptide is formed from the cleavage of proinsulin, with insulin also being produced in equal amounts. C-peptide, unlike insulin, has negligible hepatic clearance, making it a useful method for assessing pancreatic β -cell function and, therefore, measuring insulin secretion, which importantly decreases in T1D.² In type 2 diabetes (T2D), there is an inadequate response to the insulin hormone, so many of these patients take oral medications to control their glucose levels. If these medications are insufficient, exogenous insulin injections may be required. Although exogenous insulin aids in controlling glycemia in both patients with T1D and T2D, it cannot replace the β -cells' specialized function of metabolic glucose regulation. If not properly treated, diabetes can cause acute complications, such as hypoglycemia, ketoacidosis, and hyposmolar nonketotic coma, as well as chronic complications, including nephropathy, cardiovascular disease, and retinopathy.³ Historically, clinical pancreas and islet transplants have

resulted in promising outcomes for patients with T1D and poor glycemic control, although the scarce donor supply and the need for complex surgeries have limited the widespread implementation of these treatments.¹ Thus, therapy with stem cell–derived insulin-producing cells has emerged as an alternative solution, as it can enable the withdrawal of insulin therapy and overcome many of the barriers of limited donor supply. However, the ideal stem cell treatment timeline is currently unclear, with many patients requiring intermittent treatments to achieve long-term results.^{4,5}

Similar to in organ transplants, cells from Human Leukocyte Antigen (HLA)-matched donors decrease the chance of graft-versus-host disease in the recipient, so siblings and other family members are often the preferred source for these regenerative cells.⁶ But, even if an HLA-matched donor is found, the clinical adoption of stem cell therapy is complicated by significant regulatory and socioeconomic barriers. They are not currently approved by insurance because of their experimental nature and lack of US Food and Drug Administration approval for the indication of diabetes. For low-income populations, this often results in limited access to this novel treatment, further exacerbating health disparities in diabetes care. Addressing these issues through policy reform and pricing strategies will be critical for ensuring that breakthroughs in medicine translate into equitable health care solutions.

To date, embryonic, hematopoietic, neural, human umbilical–derived, and adipose stem cells have been studied as treatments for T1D and T2D. By reviewing current research on stem cell–based therapies for diabetes while emphasizing special considerations in obtaining insulin-producing cells (IPCs) from various precursor cells, we aim to illuminate the ideal stem cell for future diabetes treatment research. After carefully analyzing the availability, ethics, cost, efficacy, and adverse effects of cells from each extraction location, we argue that umbilical cord and adipose mesenchymal cells are the most promising treatments for T1D and umbilical cord stem cells are the most promising treatment for T2D.

Human-Induced Pluripotent Stem Cells and Embryonic Stem Cells

Human pluripotent stem cells (hPSCs) include embryonic stem cells and human-induced pluripotent stem cells and show promise for both T1D and T2D treatment. Human embryonic stem cells (hESCs) are derived from the inner cell mass of the embryo, and human-induced pluripotent stem cells (hiPSCs) are derived from reprogrammed adult somatic cells that function in an embryoniclike pluripotent state.¹ hESCs have self-renewal capacity, genomic stability, and can lead to all 3 germ lineages: endoderm, mesoderm, and ectoderm.⁷ Though hiPSCs possess a similar capacity for self-renewal and

differentiation, their genomic stability is uncertain.¹ Nevertheless, the use of hiPSCs has fewer ethical considerations and a minimized risk of triggering an allogenic immune response than hESCs.

The general protocol for creating IPCs from hPSCs is based on imitating the *in vivo* development of the embryonic pancreas.¹ By adding cytokines and signaling modulators to each stage of pancreatic development, specific signaling pathways that are involved in the generation of adult β -cells can be activated or inhibited, thereby allowing the hPSC to be manipulated into the β -cell phenotype.⁸ In a critical study, Rezania et al⁸ reported the successful differentiation of hESCs into IPCs using a 7-step protocol mimicking the aforementioned process. They demonstrated that the timed application of specific signaling modulators—including ALK5 and BMP receptor inhibitors, thyroid hormone (T3), and a Notch inhibitor—guided the progression of hESCs through pancreatic progenitor stages and ultimately induced insulin expression.⁸

The 2 significant challenges of transplanting hESCs are immunogenicity and teratogenicity. To mitigate these risks, their transplant necessitates an immunoisolation device and/or immunosuppressive agents.¹ A study by Henry et al⁹ reported on the use of ViaCyte, an immunoprotective delivery device, for islet cell replacement in patients with T1D.¹ This evaluation focused on a phase 1/2 prospective, multicenter, open-label trial that investigated the safety and efficacy of this device.⁹ The first encapsulation device was developed to shield pancreatic progenitor cells from immune responses, preventing reactions from foreign organs and autoimmune rejection, thereby removing the need for immunosuppressive drugs.¹ Although the first 19 patients were reported to tolerate the product well with few complications, cell survival was ultimately variable because of a foreign body response to the encapsulation device itself.⁹ ViaCyte initiated a second trial in 2017, which introduced an alternative encapsulation device with a different membrane that did not provide immune protection and involved immunosuppressants.¹⁰ The implantation of these pancreatic endoderm cells (PEC-01) was well-tolerated with no teratoma formation or severe graft-related adverse events, but only 13% of patients spent more time in the target blood glucose range.¹⁰ Although the study provided evidence that stem cell-derived endoderm cells can be transplanted into patients with T1D and successfully differentiate into islet cells, the study did not report total insulin independence in any participants. Achieving insulin independence generally requires an average meal-stimulated C-peptide of 1000 to 1500 pM, with some studies suggesting that stimulated C-peptide of only 20% of normal may be sufficient to achieve insulin independence.¹⁰ It is also important to recognize that the drawback of this new encapsulation device lies in

the necessity of immunosuppression, and ultimately, there is a compromise between a lifelong reliance on immunosuppressive agents vs recurrent administration of insulin.

Another relevant consideration surrounding the use of hESCs involves their origin. hESCs are derived from human embryos, typically from surplus embryos during in vitro fertilization procedures. A primary ethical concern surrounding hESC research is the destruction of human embryos during extraction, raising concerns for many prolife groups who consider life to begin at conception and likely creating barriers to widespread implementation of hESC treatments even if proven efficacious. Ethical guidelines, regulations, and committees aim to address these concerns by establishing standards for the ethical conduct of hESC research, ensuring informed consent and oversight in embryo donation and research protocols.¹¹ One of the primary advantages of using hiPSCs is that they bypass the need for the destruction of human embryos, making them a more appealing alternative to hESCs.

Hematopoietic Stem Cells

Bone marrow stem cells can be classified as either mesenchymal stem cells (MSCs) or hematopoietic stem cells (HSCs). HSCs can differentiate into any blood cell of myeloid or lymphoid lineage. Bone marrow stem cell transplant was first shown to be a potential treatment for diabetes in mice.¹² Since then, there have been notable advancements in the use of HSCs for treating T1D and T2D.

Research studying HSC transplant for T1D began with the attempt to regenerate destroyed pancreatic β -islet cells. Kang et al¹³ sought to determine whether HSCs could differentiate into pancreatic islet cells in vivo. They found that, while transplant prevented the onset of diabetes in all their mice models, only 1 mouse out of 45 with T1D became fully insulin independent following the transplant. There was no evidence to suggest that HSCs promote the regeneration of destroyed pancreatic islet cells once the diabetes was established, but complete donor chimerism was achieved in all their long-surviving mice, suggesting that the transplanted HSCs were successfully able to be integrated into the host's existing immune system.¹³ In a study by Voltarelli et al¹⁴ that measured exogenous insulin usage, C-peptide levels, and antiglutamic acid decarboxylase antibody titers for patients with T1D who underwent HSC transplant with concurrent immunosuppressive medications, 14 of the 15 patients were insulin free for at least 1 month and 12 were insulin free for over 6 months.

In a follow-up study by the same group, 8 additional patients were added to the original 15 and complete insulin independence was observed in 20 patients with no history of ketoacidosis or concomitant corticosteroid usage during the preparative regimen.¹⁵ Of these 20, 12 patients remained insulin

free for an average of 31 months.¹⁵ There were 8 patients whose T1D relapsed and they resumed low-dose insulin.¹⁵ Eight of 16 patients in these 2 studies reported adverse effects, such as febrile neutropenia, nausea, vomiting, pneumonia, and oligospermia.^{14,15}

In another study, the relapse rates were more significant, and the long-term efficacy of autologous nonmyeloablative HSC transplant (AHSCT) was questioned.¹⁶ Of 40 participants, 20 received AHSCT, and the remaining 20 received insulin-only treatment.¹⁶ Fourteen participants in the experimental group became insulin independent (compared with 1 in the control group) for 1.5 to 48 months, but 11 patients relapsed within 19.5 months.¹⁶ At 4-year follow-up, researchers reported that the difference in daily insulin dosages between the AHSCT and control groups decreased.¹⁶ This study demonstrated that AHSCT may not be effective for the long-term treatment of T1D and that relapse is common.

Compared with treatment for T1D, HSC treatment for T2D is less conclusive. Estrada et al¹⁷ observed improvements in glycemic control and C-peptide levels resulting in reduced insulin requirements in patients with T2D. Their experiment combined autologous bone marrow stem cell treatment with hyperbaric oxygen treatment, which has been shown to increase stem cell mobilization to sites of injury for pancreatic islet cell repair and to potentially provide anti-inflammatory effects.¹⁷ After 25 participants with T2D underwent 5 daily hyperbaric oxygen sessions pre- and post- stem cell infusion, 9 participants reduced their daily insulin dosage by more than 50%, while 3 patients needed to increase their oral hypoglycemic medication.¹⁷ Although the study demonstrated decreases in fasting glucose levels and an associated rise in C-peptide levels, more research is needed to support this stem cell strategy for people with T2D.

Cost and feasibility are important treatment considerations for HSC transplant and AHSCT. AHSCT is costly and can only be done in specialized bone marrow transplant facilities. Paired with the high rates of relapse, repeated transplants may not be an affordable option for many patients. To address these limitations, a study by Cantú-Rodríguez et al¹⁸ explored the possibility of outpatient AHSCT by designing a protocol around fludarabine. In 16 patients with early-onset T1D, 7 patients achieved insulin independence, 6 had transient insulin independence, and 3 demonstrated no response to the treatment. The 7 patients who achieved complete insulin independence maintained this status until the last follow-up at 56 months. Although these results are limited, this protocol lays a promising foundation for future research into using HSCs for diabetes treatment.

Neural Stem Cells

Adult neural stem cells (NSCs) have also shown promise as a future diabetes treatment. Derived from both the olfactory bulb and hippocampus, these cells and their associated progenitors were traditionally targeted as potential treatments for neurodegenerative diseases such as Alzheimer and Parkinson diseases.¹⁹ However, a study conducted by Kuwabara et al²⁰ on rodents with diabetes determined that NSCs also spur insulin production in the brain and in allogeneic pancreatic tissues following transplant, making them a potential candidate for curative therapy. This study isolated olfactory bulb and hippocampus stem cells from recently deceased rat brain tissues and cultured them to stimulate cell differentiation into olfactory bulb and hippocampus neuronal lineages.²⁰ These differentiated progenitor cells showed markedly increased levels of insulin gene expression.²⁰ Then, after confirming C-peptide reactivity to glucose in a similar sample of NSCs derived from rodents with T1D and T2D, olfactory bulb and hippocampus collagen grafts were transplanted into the pancreatic splenic lobes of a new population of similarly affected rats.²⁰ These grafts “reduced blood glucose and up-regulated insulin levels” until the graft was removed, which provides evidence for a relationship between neural stem cell activity and glucose regulation.²⁰

These encouraging results support further investigation into testing both human and animal models, but the many obstacles surrounding NSC extractions have stunted this research. Compared with other types of stem cells, adult NSCs must be obtained from mature human brains, making them relatively inaccessible without excessively invasive measures.²¹ In one study, brain tissue removed from patients during surgery for temporal lobe epilepsy was donated as a source of NSCs, but even if these samples had ultimately provided effective allograft tissues, the small supply would likely be impractical for widespread use in a common condition like diabetes.²¹ Other recent research has attempted to isolate NSCs from fetal tissue or derive them from MSCs, each of which brings additional ethical and tumorigenic considerations.²² But, when using cells that are already differentiated and are gathered from adults, NSCs avoid the problems associated with embryonic cell waste after failed cell differentiation.²³ For this reason, extracting adult cells involves less ethical considerations than using embryonic stem cells, although NSCs have consistently been proven difficult to populate in high concentrations even after being gathered.^{21,23}

If safe and practical methods are developed to harvest NSCs, the potential benefits of these cells may be better realized in humans. This is particularly likely for olfactory bulb NSCs, which are accessible through an endonasal approach, compared with those from the hippocampus, which lie much deeper in the brain.^{20,24} Currently, the barriers associated with cell extraction

make NSCs less likely than other stem cell types to be implemented on a national scale if they are proven to be effective for treating diabetes in humans.

Umbilical Cord–Derived Stem Cells

Umbilical cord–derived stem cells (UC-MSCs) are MSCs, a subtype of multipotent stem cells, that are currently under investigation as a viable treatment modality for T1D and T2D in ongoing clinical trials due to their demonstrated efficacy, safety, abundance, and the minimal ethical considerations associated with their use.²⁵ Several recent investigations have underscored the effectiveness of UC-MSCs in treating T1D. Each of the studies discussed had between 1 and 4 infusions of UC-MSCs that were normalized by each participant's body weight. Additionally, each study used stem cells from either a single human donor umbilical cord or from multiple HLA and sex-matched donors. A study by Lu et al⁵ reported that when treating patients with T1D with 2 UC-MSC transplants spaced 3 months apart, 40.7% of treated patients achieved the primary end point of a 10% increase in fasting C-peptide levels at 1-year follow-up. These findings were corroborated by Carlsson et al,⁴ who observed a 47% reduction in C-peptide levels in placebo-treated patients compared with a 10% decrease in patients treated with a single dose of UC-MSCs upon 1-year follow-up. This indicates a significant preservation of β -islet cells and insulin production.

Additionally, Wu et al²⁶ investigated the cotransplant of UC-MSCs and bone marrow in T1D treatment and performed a follow-up 8 years after treatment. Their study demonstrated a sustained increase in endogenous insulin production, a reduction in T1D-associated adverse events, and a positive overall safety profile.²⁶ Together, these 3 publications present recent additions to an ever-growing body of work demonstrating the safety and efficacy of umbilical stem cells in the treatment of T1D.^{4,5,26}

Numerous studies have also demonstrated the efficacy of UC-MSCs in T2D. Zang et al²⁷ used retrospective continuous glucose monitoring to detect changes in time in range and glycosylated hemoglobin A_{1c} (HbA_{1c}) in patients with T2D treated with UC-MSCs. While both treatment and placebo groups exhibited significant improvements in time in range and HbA_{1c} from baseline, the treatment group demonstrated a greater change in time in range and HbA_{1c} levels.²⁷ Similar results were reported in another study by Zang et al,²⁸ which demonstrated the efficacy and safety of UC-MSC treatment in Chinese adults with T2D. This trial found that 20% of the treated group achieved an HbA_{1c} level less than 7% and a 50% or greater reduction in daily insulin dosage compared with 4.55% of the control group.²⁸ Additionally, Lian et al²⁵ reported significant reductions in fasting plasma glucose levels and HbA_{1c} levels following UC-MSC treatment for

T2D, along with noted improvement in β -islet cell function. Collectively, these studies underscore the safety and efficacy of UC-MSC treatment in T2D.^{25,27,28}

Another major advantage of using UC-MSCs is the source of the tissue from which they are derived. Because UC-MSCs are harvested from the umbilical cords of donors after birth, their use raises fewer ethical concerns compared with embryonic stem cells. Tissue that would otherwise be discarded can instead contribute to the treatment of a wide range of diseases. Cai et al²⁹ described the processes of extraction, isolation, and culturing in detail.

Adipose-Derived Stem Cells

Adipose-derived stem cells (ADSCs) are another type of MSC that are currently being investigated in clinical trials as a therapeutic avenue for T1D.^{25,30} However, to our knowledge, there is a lack of recent clinical trials involving ADSCs in treating T2D. Nevertheless, several recent studies have exhibited the efficacy and safety of ADSC-based therapies. In each of the studies discussed, participants received a single dose of ADSCs. Adipose cells were isolated from unrelated donors and characterized via Polymerase Chain Reaction (PCR) before differentiation. Analogous to UC-MSCs, ADSCs are abundant, easily accessible, and pose minimal ethical concerns, rendering them attractive candidates for therapeutic development.^{4,30}

Multiple studies have demonstrated safety and efficacy for ADSC transfusions in T1D treatment. Thakkar et al³¹ provided an initial successful report of co-infusion of autologous vs allogeneic ADSCs and bone marrow-derived hematopoietic stem cells for T1D treatment. Both treatment groups exhibited sustained improvements in HbA_{1c} and C-peptide levels, along with reductions in glutamic acid decarboxylase antibodies and insulin requirements.³¹ Araujo et al³² conducted a pilot study treating patients with recently diagnosed T1D with ADSCs and vitamin D, demonstrating increased stability of C-peptide, improved glucose control, and reduced insulin requirements compared with controls at 3-month follow-up. This was corroborated by Dantas et al,³⁰ who also treated patients with ADSCs and vitamin D, observing absolute increases in basal C-peptide levels and improvements in HbA_{1c} levels at 6-month follow-up. Notably, minimal or transient adverse effects were reported in these trials.³⁰⁻³² Each study contributes to the growing body of evidence supporting ADSCs as a potentially safe and efficacious treatment option for individuals with T1D.³⁰⁻³²

Conclusions

A variety of stem cell populations have demonstrated promise for future T1D and T2D therapy, including embryonic, induced pluripotent, hematopoietic, neural, and mesenchymal stem cells. Along with differences in efficacy, each

category varies in anatomic location and safety profile, adding layers of complexity to evaluating their roles in future treatment regimens. To demonstrate clinical benefits over exogenous insulin, a holistic patient-centered approach is necessary to safely and ethically restore complete insulin independence without the need for frequent injections or harmful long-term immunosuppressive therapy.

Regarding human efficacy in treating patients with T1D, bone marrow hematopoietic cells, umbilical cord mesenchymal cells, and adipose-derived mesenchymal cells demonstrated the strongest potential for long-term endogenous glycemic control following treatment.^{15,26,32} However, especially when using bone marrow stem cells, the magnitude and duration of these impacts vary widely between patients and commonly result in eventual relapse.¹⁶ In patients with T2D, bone marrow and umbilical cord mesenchymal cells have currently exhibited the most effectiveness.^{17,25} Because other stem cells, such as those from brain tissue, have been successful in mouse models, additional human testing of all stem cell types is necessary to determine the most effective stem cell for treatment.²⁰

Another factor impacting treatment is the surgical accessibility and donor availability of stem cell tissues. While umbilical cord, adipose, and embryonic tissues are readily available and easy to access for physicians, harvesting bone marrow and NSCs is typically more invasive and difficult.^{4,14,21,30} Because diabetes is common, large amounts of donor tissue will be necessary for the eventual widespread implementation of a proven stem cell treatment, making this consideration important. Future innovations in harvesting and cell replication techniques will likely make stem cell treatments less challenging for physicians and more affordable for patients.

Other considerations include the ethical questions surrounding the use of embryonic cells and the possible harms of using immunosuppressive therapy, which can increase the severity of infections, especially during hematopoietic and pluripotent stem cell treatments.^{1,14} These, paired with the aforementioned variations in efficacy and surgical accessibility, point to HLA-matched umbilical cord and adipose mesenchymal cells as being the most promising stem cell types for T1D and HLA-matched umbilical cord stem cells as the most encouraging for T2D. Even so, further research is necessary to establish long-term clinical effectiveness over exogenous insulin injections and to justify Food and Drug Administration approval of stem cell treatments for diabetes.

As stem cell therapies for diabetes continue to become more effective, efficient, and readily available, they will continue to have greater impacts on the clinical management of this chronic condition. By combining them with other therapies, such as hyperbaric oxygen to increase cell mobilization and encapsulation devices to prevent immune rejection, researchers continue to search for an ideal treatment protocol that demonstrates consistent long-term

benefit.^{9,33} As demonstrated by existing research, stem cells from a variety of extraction locations have shown promise for curative treatment, but there continues to be a lack of existing data on large patient populations due to the logistical, anatomical, financial, ethical, and postoperative challenges these treatments currently present to the medical community.³⁴ While stem cells provide no immediate threat to exogenous insulin injections or other management medications, they represent an emerging modality with the potential to fundamentally reshape future diabetic therapy as technology continues to advance.

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Conflicts of Interest

The authors have no competing interests to declare.

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