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Stem Cell Therapy for Type 1 Diabetes

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Abstract

Type 1 diabetes is an increasingly widespread autoimmune disorder that destroys the insulin-producing cells of the pancreas. Without insulin, the cells cannot insert glucose transporters into their membrane and blood sugar subsequently rises. The effects of type 1 diabetes can develop into various life-threatening conditions including heart attacks and strokes. Insulin therapy is required for type 1 diabetics, but its short-lived effects are less than ideal and often decrease quality of life. Stem cells offer a long-term solution with their ability to differentiate into insulin-producing beta cells and modulate the immune system. They can be injected directly into the body or implanted in encapsulated devices. Regardless of the technique, stem cells can restore insulin production in the body and offer a potential cure for type 1 diabetes. Stem cell therapy has a list of benefits, but the advanced technology will inevitably come with a high price tag, contributing to the increasingly inaccessible treatment options for type 1 diabetes. Should future success convince the FDA to approve its clinical use and convince insurance to cover the procedure, the long-term solution of stem cell therapy might replace insulin injections forever.

Keywords

Type 1 diabetes; Beta cells; Stem cells Encapsulated device; CRISPR-Cas9.

Abbrevations

- BM-derived MSCs- Bone marrow-derived mesenchymal stem cells
- CRISPR-Cas9- Clustered regularly interspaced short palindromic repeats and CRISPR-associated protein 9
- FDA- Food and Drug Administration
- GAD- Glutamic acid decarboxylase
- GLUT4- Glucose transporter type 4
- HbA1C- Hemoglobin A1C
- Ipf-1- Insulin promoting factor-1
- Isl-1- Insulin gene enhancer protein 1
- MSCs- Mesenchymal stem cells
- Pax-6- Paired box 6
- PEC- Pancreatic endoderm cells
- T-reg- T-regulatory
- T1D- Type 1 diabetes

Introduction

Acting as both an endocrine and exocrine gland, the pancreas plays an important role in digestion. During its exocrine role, the pancreas releases enzymes in the form of pancreatic juices to break down food in the small intestine [1]. As the food is digested, glucose is absorbed into the bloodstream where it is delivered to the body's cells. The endocrine portion of the pancreas detects the increase in blood glucose and subsequently secretes insulin. Insulin is a hormone that initiates the insertion of GLUT4 (glucose transporter type 4) transporters into the plasma membrane, allowing glucose to enter the cell [2]. Not only does glucose uptake supply the cells with energy, it preserves the integrity of blood vessel walls by maintaining healthy levels of blood sugar [3]. In an increasing number of individuals, this process has gone awry at the hands of their own body.

Type 1 diabetes (T1D), also known as juvenile or insulin-dependent diabetes, is an autoimmune condition in which the body's immune cells attack the insulin-secreting beta cells of the pancreas [4]. In the absence of beta cells, the pancreas is unable to produce insulin and glucose accumulates in the blood. Healthy blood sugar levels range from 80-130 mg/dL before eating, and anything less than 180 mg/dL two hours after eating [5]. Diabetics reach glucose levels much higher, increasing their risk for heart attacks, strokes, neuropathy, kidney failure, diabetic retinopathy, and severe infections [5]. The exact cause of T1D is unknown, however, it could be the result of a viral infection or a genetic predisposition that triggers the autoimmune response. Unlike type 2 diabetes, T1D is not a result of diet or lifestyle [5]. Therefore, preventing its onset remains close to impossible.

Treatment involves a lifetime of insulin injections alongside lifestyle changes that maintain normal blood glucose levels including a healthy diet, exercising, maintaining a healthy weight, and counting carbohydtrates, fats, and proteins [5]. Although the disease is manageable, the frequency at which type 1 diabetics monitor their blood sugar and administer insulin significantly decreases their quality of life. T1D is only becoming more prevalent, as 8.4 million people currently suffer from the disease worldwide, and at least 5.1 million more are expected to be diagnosed by 2040 [6]. Because the disease is quickly

increasing in prevalence and the effects of its current treatment are short-lived, many researchers are on the hunt for a long-term solution for T1D, and they may have just found it.

Discussion

Current and prospective treatments for T1D suffer from inefficiency and inaccessibility. Insulin is a life-long treatment that requires frequent monitoring and a pretty penny. Pancreatic islet transplants, although seemingly promising, are at a standstill due to Food and Drug Administration (FDA) and insurance approval, limited donor supply, and demanding patient qualifications [7]. On the horizon is cellular therapy, where stem cells are gaining popularity for their ability to differentiate and self-renew. Because stem cells can transition from an ordinary cell to a highly specialized one, they could potentially treat diseases that originate from the loss of a key anatomical component. Differentiated beta cells can replace those that were lost from the autoimmune response of T1D, theoretically restoring the endocrine function of the pancreas [7].

Differentiation of MSCs into insulin-producing cells

To recover the beta cells lost in T1D, S. Dave and others injected both autologous adipose tissue-derived mesenchymal stem cells (MSCs) and bone marrow-derived hematopoietic mesenchymal stem cells (BM-derived MSCs) into 10 patients [8]. The adipose tissue-derived MSCs were to be differentiated into beta cells. Various factors like C-peptide, HbA1C (hemoglobin A1C), glutamic acid decarboxylase (GAD) antibody levels, and Pax-6 (paired box 6), Ipf-1 (insulin promoting factor-1), and Isl-1 (insulin gene enhancer protein 1) transcription factors were used as measures of efficacy. C-peptide is indicative of insulin production in the body. HbA1C is a measure of glucose bound to hemoglobin in blood. GAD antibodies are found in patients with diabetes, which target GAD enzymes in the body [9]. Lastly, Pax-6, Ipf-1, and Isl-1 transcription factors are involved in the development of insulin-producing pancreatic cells [10].

All 10 patients showed improvements in C-peptide, HbA1C, blood sugar, and insulin injection requirements after an averaged 32-month follow-up [8]. C-peptide levels increased from the initial level, indicating insulin production in the body. HbA1C decreased following the stem cell transplant, suggesting a reduction in the amount of glucose bound to hemoglobin and therefore an increase in glucose uptake by the cells. On that same note, fasting blood sugar and postprandial (after meal) blood sugar decreased by the end of the trial. The amount of exogenous insulin required by patients also decreased by nearly half, as the patients were beginning to produce their own insulin. Additionally, the amount of GAD antibodies decreased by nearly two-thirds, becoming more representative of non-diabetic patients following stem cell therapy. Lastly, evidence of Pax-6, Ipf-1, and Isl-1 transcription factors in the MSCs suggests that they differentiated into insulin-producing cells as intended (Figure 1) [8].

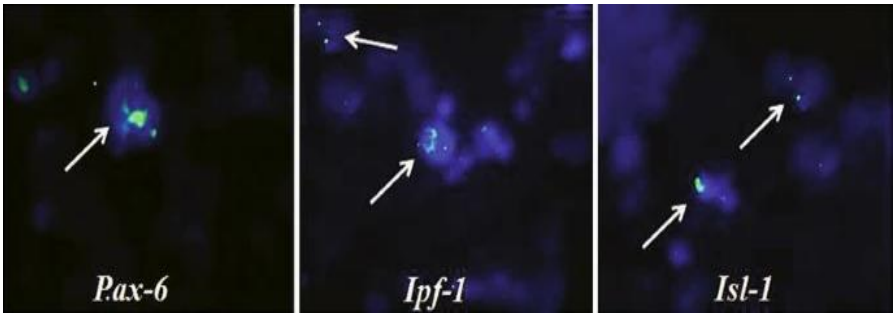

Figure 1: Evidence of Pax-6, Ipf-1, and Isl-1 transcription factors in insulin-secreting cells following stem cell injection [8].

The Immunomodulatory Effects of MSCs

Although some success has been made in the replacement of beta cells with stem cells, the goal for treating T1D may not be restoring the loss of function but rather addressing the autoimmune response that leads to it. In other words, replacing the dysfunctional beta cells may not reverse T1D if the immune system will just attack them again. No worries– stem cells have that covered, too. As mentioned previously, MSCs are noted for their immunomodulatory abilities, meaning they can regulate the activity of the immune system by altering immune cell functions [11]. MSCs also lack immunogenicity so that they can regulate the immune system while simultaneously going undetected [12]. These multipotent stem cells are easily collected in large quantities, making them accessible for both research and treatment [13].

In a clinical trial published in 2022, M. Izadi and others investigated the ability of MSCs to target the autoimmune response of T1D via immune regulation and regeneration [14]. Since the MSCs are simply regulating the immune system rather than differentiating into insulin-producing cells, this trial is intended for patients who still have functional beta cells remaining. During phase I, an experimental group received autologous BM-derived MSCs at weeks 0 and 3, and a control group received a placebo at weeks 0 and 3. Phase II began one year later, where both the experimental and control groups received a dose of BM-derived MSCs. The original experimental group was aptly renamed to the early treatment group, and the control group to the late treatment group as their stem cell dose was delayed by a year. MSC efficacy was measured by fasting blood sugar, 2-hour postprandial glucose test (after eating), C-peptide levels, HbA1C levels, required exogenous insulin, and lability index. Additionally, this study investigated the safety of stem cell therapy for T1D by measuring hypoglycemic events (blood sugar below 70 mg/dL). This is common in type 1 diabetics as improper insulin dosage can overshoot the body's needs, causing the cells to take up too much blood glucose [15].

By the end of phase I, the total number of hypoglycemic events (including grades I-V) declined in the experimental MSC group compared to the placebo group, suggesting that stem cell therapy is inherently safer than traditional insulin therapy [14]. Phase II, however, found that only grade II hypoglycemic events (blood glucose less than 55-40 mg/dL) were statistically lower in the early treatment group compared to the late treatment group. Thus, the ability of MSCs to prevent hypoglycemia does not change following the initial year of transplantation. In phase I, MSCs did not significantly improve resting or postprandial

blood glucose levels, the amount of exogenous insulin required, or the amount of insulin produced compared to the placebo. HbA1C levels, however, were reduced by MSCs in comparison to the placebo group. As for the metabolic effects of phase II, fasting blood sugar, 2-hour postprandial sugar, exogenous insulin/insulin injections, and lability index were not statistically different between the early treatment group and the late treatment group. However, C-peptide levels appear to be higher in the early treatment group compared to the late treatment group, suggesting that insulin production increases over time with MSC therapy. On that same note, HbA1C levels were lower in the early treatment group than the late treatment group, indicating that longer stem cell treatment further reduces the amount of glucose attached to hemoglobin in the blood [14].

The immunomodulatory effects of MSCs appear promising as anti-inflammatory cytokines and T-regulatory (T-reg) cells increased while pro-inflammatory cytokines decreased after one year compared to the placebo [14]. Because inflammation is evidence of a functioning immune system, its suppression indicates that the autoimmune response is effectively reduced by the MSCs, treating the source of T1D. Additionally, increased T-reg cells suggest that the immune response was dialed down one year following MSC injection. As the MSC patients progressed through phase II, they experienced lower pro-inflammatory cytokine levels and higher anti-inflammatory cytokines compared to the late treatment group, indicating that the suppression of the autoimmune response improves with longer durations of stem cell therapy [14].

In summary, MSCs are a potential candidate for T1D treatment as immune system regulators. In those with recently diagnosed T1D, early suppression of the autoimmune response by MSCs can protect the patient's remaining beta cells, allowing the pancreas to produce insulin independently. However, individuals who have had T1D for a longer period may not have enough functional beta cells remaining for this technique to be effective. In this case, stem cells might be more beneficial as a mechanism to replace the beta cells via differentiation.

Stem Cell Encapsulated Devices

A novel method of transplantation has been pioneered that could effectively deliver stem cell-derived beta cells through encapsulated devices (Figure 2). The semipermeable membrane surrounding the device allows for perfusion and the passage of nutrients, oxygen, glucose, and insulin [16]. Ideally, the membrane would be impermeable to the body's immune cells to prevent immune rejection, as the alternative of immunosuppressant drugs leaves patients vulnerable to infection. Companies like ViaCyte and Vertex are working towards an effective, long-term encapsulated device that might someday cure T1D.

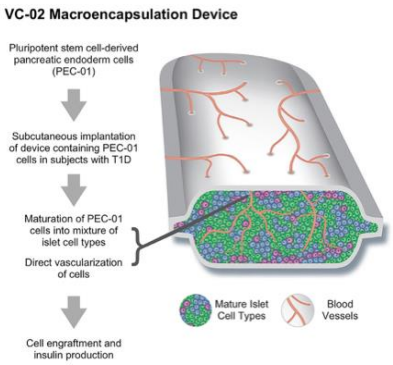

Figure 2: Encapsulated PEC-Direct device containing stem cell-derived pancreatic beta cells with a semipermeable barrier for both exchange and protection [17].

ViaCyte primarily uses embryonic stem cell-derived pancreatic endoderm cells (PEC) in their implants, which differentiate into insulin-secreting cells following transplantation [18]. They have tested a variety of encapsulated devices including PEC-Direct, PEC-Encap, and PEC-QT. ViaCyte has recently conducted a clinical trial to determine the safety and efficacy of PEC-Direct (VC-02), a subcutaneous implantation containing pluripotent embryonic stem cell-derived PECs (Figure 2) [19]. Long-term type 1 diabetics received PEC-Direct implants and were monitored for 1 year. The membrane of the device did not repel the body's immune cells, so the patients received immunosuppressants to prevent rejection.

By the end of the trial, there was an overall increase in both fasting and postprandial C-peptide levels, marking the production of insulin [19]. After removing the device from the patients, fluorescent markers were able to detect insulin-immunoreactive cells within the implant. In other words, the stem cell-derived pancreatic cells successfully matured into the beta cell phenotype in vivo. Additionally, the patients experienced a 20% reduction in required exogenous insulin since the stem cells began producing insulin within the device. Because the body's cells were now signaled to take up glucose from the bloodstream, patients spent more time within the target blood glucose range. Lastly, the patients in this trial experienced an improved quality of life and reduced rates of diabetic complications. This study supports the notion that stem cell-derived PECs can differentiate into functional beta cells within an encapsulated device [19].

To address the pitfalls of PED-Direct's membrane permeability, ViaCyte created another encapsulated device with the capacity to protect against the immune system called PEC-Encap (VC-01) (Figure 3). PEC-Encap consists of an Encaptra membrane that shields the device from immune cells, eliminating the need for immunosuppressant drugs [20]. In addition to protecting the stem cells from the immune response, the encapsulated device also allows for the exchange of nutrients and wastes [20].

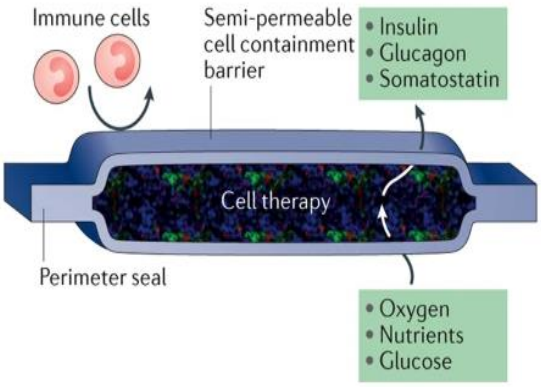

Figure 3: Visual representation of the PEC-Encap device containing beta cells surrounded by a semipermeable barrier permeable to nutrients, gasses, and hormones, but impermeable to immune cells [21].

The first PEC-Encap clinical trial began in 2014 to determine the safety and efficacy of immune protective devices in treating T1D [22]. There were two treatment groups in this clinical trial: one group received 2 VC-01 implants and the other group received 4-6 VC-01 implants [23]. C-peptide levels were to be measured as an indicator of insulin production by the differentiated stem cells. During the trial, fibrosis surrounded the PEC-Encap device and caused the stem cells to die [22]. Portions of the implant's membrane were vascularized, but not enough to be considered a success as perfusion is required for nutrient and waste exchange between the device and the body [24]. As a result, the trial was canceled prematurely and ViaCyte went back to the drawing board.

A few years later, ViaCyte partnered with W.L. Gore and Associates to test a newly modified PEC-Encap device encapsulated by a polytetrafluoroethylene membrane [24]. This design should prevent immune rejection as well as promote angiogenesis, or the formation of blood vessels. Again, perfusion of the implant is essential for the exchange of nutrients and other materials. Patients received 12 implants in the absence of immunosuppressants to test the efficacy of insulin-producing stem cells and the polytetrafluoroethylene membrane [24]. Although the trial was expected to end in late 2022, its status remains "active" [25]. We might be able to see the results as early as 2023 [26]. As this implant's design accounts for both insulin production and the prevention of immune rejection, the results are highly anticipated among researchers and physicians alike.

ViaCyte is continuing to expand the horizons of T1D stem cell therapy by partnering with CRISPR Therapeutics. Thus far, evading the immune response has required external protective measures. What if you could instead genetically alter the stem cells into a 'native' cell, eliminating the need for immunoprotection? ViaCyte and CRISPR Therapeutics are doing just that with the new PEC-QT device. CRISPR Therapeutics is responsible for genetically modifying the stem cells' genome to make them invisible from the body's immune system [24]. Gene editing is done using CRISPR-Cas9 technology (Clustered Regularly Interspaced Short Palindromic Repeats and CRISPR-associated protein 9). A molecular pair of scissors known as Cas9 is guided to a specific section of DNA where it can cut and edit the sequence. In the case of T1D therapy, CRISPR-Cas9 turns off the beta2-microglobulin gene and turns on the programmed death-ligand transgene, which collectively stops the attack of immune cells [24].

ViaCyte is responsible for differentiating these genetically modified stem cells into insulin-producing cells (Figure 4) [27]. Like other PEC implants, these genetically altered stem cells are placed into an encapsulated device that is then implanted into the patient. Once in the body, the stem cells will complete their differentiation into insulin-producing beta cells and the device will eventually become vascularized for nutrient and waste exchange.

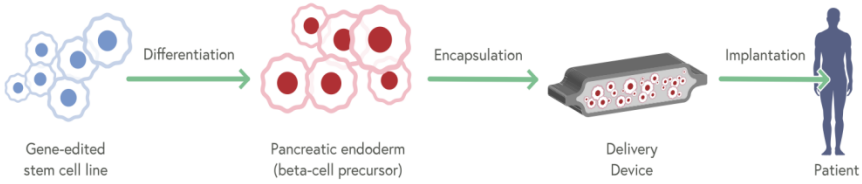

Figure 4: CRISPR-Cas9 modified stem cells transplanted to a patient in an encapsulated device [27].

This design can potentially overcome the drawbacks of other PEC-Encap trials, where the device itself is responsible for protecting the stem cells from immune attack. It is also an improvement from the PEC-Direct implant which has no immune protective elements and requires external immune suppression through drugs, leaving patients susceptible to infections. According to ViaCyte's chief medical officer Dr. Howard Foyt, grouping the stem cells together in a single device allows them to be easily removed if the patient were to have an unexpected immune response to it [28]. Additionally, the implant is anticipated to last anywhere from 5-10 years at which time the patient will need a replacement [28]. Although the device itself is not permanent, an implanted device that automatically produces insulin for type 1 diabetics is a significant improvement from daily insulin injections.

In early 2022, ViaCyte and CRISPR Therapeutics transplanted the PEC-QT device into their first patient [29]. As they have split the trial into two phases, the earliest set of results are expected to be published within the next year or so. The second half of the trial and other concluding remarks may be published by 2025 [26]. The results are highly anticipated as this device could be a long-term treatment for T1D without additional immunosuppression. ViaCyte has made great strides in the realm of T1D stem cell therapy with three implant devices. PEC-Direct has been tested in clinical trials where C-peptide levels indicated insulin production in type 1 diabetics. However, PEC-Direct requires immunosuppression, which makes it less desirable as a potential therapy. PEC-Encap is being investigated to overcome the need for immune suppression by creating a protective barrier from the body's immune system. PEC-QT may be the next best thing, eliminating the need for an immune barrier by CRISPR-Cas9 genome editing. Not only are the stem cells differentiated into insulin-producing cells, but they are also genetically modified to avoid detection by the immune system.

Vertex has also explored the use of encapsulated devices in treating T1D. Their VX-880 device is tailored to type 1 diabetics most at risk for hypoglycemia [30]. Containing allogeneic stem cell-derived pancreatic beta cells, VX-880 is implanted into the hepatic portal vein of the liver. In response to increased blood glucose levels, the differentiated stem cells release insulin into the body through the semipermeable membrane. VX-880 requires additional immunosuppression to avoid an immune attack, leaving patients

vulnerable to infection as previously discussed. The VX-880 trial is a phase 1/2 study in which 2 patients received the implant at only half the dosage in Part A, and 5 patients received the implant at full dosage in Part B [31]. More are expected to receive the full dosage of VX-880 in Part C for a total of 17 patients [31].

As of now, there have been two announced updates for the first leg of the trial. In October of 2021, Vertex announced the first 90-day update for the 2 patients being treated with half a dose of the stem cell therapy [30]. The implant was engrafted without complications, and the insulin-producing stem cells were having a beneficial effect on metabolic indices. In both fasting and postprandial conditions of one patient, C-peptide secretion had increased quickly at the start of the trial. HbA1C had also improved throughout the trial, aiding in the regulation of blood sugar and hypoglycemic events. The amount of exogenous insulin required was also reduced by over 90% as insulin production began to recover in vivo. The obvious downside to VX-880 is the lack of immunoprotection within the device, however, Vertex is working towards an encapsulated device that guards the stem cells from the immune system [30]. As of June 2022, both patients in Part A spent more time within the target blood glucose range and thus did not require as much exogenous insulin [31]. In fact, one patient no longer required insulin by day 270 as they were producing enough on their own, implying that T1D could be cured by an encapsulated device. Additionally, a third patient was given a full dose of VX-880 to begin Part B of the trial [31].

With two major companies working on stem cell encapsulated devices for T1D, competition becomes fierce. To eliminate the threat, Vertex has recently bought out ViaCyte [32]. ViaCyte has made strides in the immune protective encapsulation membrane that Vertex desires for their VX-880 implant. ViaCyte has also created different stem cell lineages and partnered with CRISPR Therapeutics. With a combination of methods, ideas, and technology, the merging of Vertex and ViaCyte might prove beneficial in the long-term treatment of T1D [32].

With stem cell therapy on the rise, it is possible that insulin may become a thing of the past. Since stem cells can be a functional replacement of the beta cells lost in T1D, they hold curative potential. The effects of insulin, on the other hand, are short-term and require repeated injections throughout the day. Despite the obvious benefits of stem cells, they share the same problem as insulin: inaccessibility. Minorities have a greater prevalence of T1D, yet they fall victim to health disparities and cannot access current treatment [33]. The cost of a single prescription of insulin has risen dramatically over the past several years as the pharmaceutical industry price gouges a vulnerable group [34]. It is unlikely that stem cells will be any more affordable considering the technology involved. For stem cell therapy to become widespread in practice, it must first become accessible to those that need it most.

Conclusion

Stem cells are highly anticipated in the long-term treatment of T1D. With the capacity to differentiate into pancreatic beta cells and modulate the body's immune system, MSCs appear to be the most promising candidate for stem cell therapy. MSCs have been found to adopt a beta cell-like phenotype and improve several metabolic indices. Additionally, MSCs' immunomodulatory properties can effectively regulate the autoimmune response, thus restoring insulin production in recently diagnosed type 1 diabetics.

Encapsulated devices may be the next big thing in the world of stem cell therapy. Now combined under one company, ViaCyte and Vertex are working towards a protective implant that allows differentiated stem cells to produce insulin while remaining hidden from the immune response. They are also exploring stem cell therapy in conjugation with genetic modification to eliminate the threat of immunity altogether. Regardless of the technique, stem cells offer an abundance of benefits, including long-term treatment and an overall improvement in health and wellbeing. There is no questioning the potential of stem cell therapy, however, it is crucial that accessibility is granted among all type 1 diabetics. If those who need it most cannot access treatment, the benefits of stem cell therapy are limited.

References

1. Jennings RE, Berry AA, Strutt JP, Gerrard DT, Hanley NA. (2015) Human pancreas development. Development, 142(18), 3126–37.
2. Leto D, Saltiel AR. (2012) Regulation of glucose transport by insulin: traffic control of GLUT4. Nat Rev Mol Cell Biol. 13(6):383–96.
3. Rask-Madsen C, King GL. (2013) Vascular complications of diabetes: mechanisms of injury and protective factors. Cell Metab. 17(1): 20–33.
4. Atkinson MA, Eisenbarth GS, Michels AW. (2014) Type 1 diabetes. The Lancet, 383(9911):69–82.
5. https://www.mayoclinic.org/diseases-conditions/type-1-diabetes/symptoms-causes/syc-20353011
6. Gregory GA, Robinson TIG, Linklater SE, Wang F, Colagiuri S, et al. (2022) Global incidence, prevalence, and mortality of type 1 diabetes in 2021 with projection to 2040: a modelling study. Lancet Diabetes Endocrinol. 10(10):741–60.
7. de Klerk E, Hebrok M. (2021) Stem Cell-Based Clinical Trials for Diabetes Mellitus. Front Endocrinol. 12: 631463.
8. Dave SD, Vanikar AV, Trivedi HL, Thakkar UG, Gopal SC, et al. (2015) Novel therapy for insulin-dependent diabetes mellitus: infusion of in vitro-generated insulin-secreting cells. Clin Exp Med. 15(1):41–45.
9. Crotti D, Selmi C. (2014) Glutamic acid decarboxylase antibody. Autoantibodies. 3:385-89.
10. Dave SD, Vanikar AV, Trivedi HL. (2014) In-vitro generation of human adipose tissue derived insulin secreting cells: up-regulation of Pax-6, Ipf-1 and Isl-1. Cytotechnology, 66(2):299–07.
11. Corcione A, Benvenuto F, Ferretti E, Giunti D, Cappiello V, et al. (2006) Human mesenchymal stem cells modulate B-cell functions. Blood. 107(1):367–72.
12. Schu S, Nosov M, O'Flynn L, Shaw G, Treacy O, et al. (2012) Immunogenicity of allogeneic mesenchymal stem cells. J Cell Mol Med. 16(9):2094–03.
13. Ding DC, Shyu WC, Lin SZ. (2011) Mesenchymal stem cells. Cell Transplant. 20(1):5–14.
14. Izadi M, Nejad SHA, Moazenchi M, Masoumi S, Rabbani A, et al. (2022) Mesenchymal stem cell transplantation in newly diagnosed type-1 diabetes patients: a phase I/II randomized placebo-controlled clinical trial. Stem Cell Res Ther. 13(1):264.
15. Mc Crimmon RJ, Sherwin RS. (2010) Hypoglycemia in type 1 diabetes. Diabetes. 59(10):2333–39.
16. Stock AA, Manzoli V, De Toni T, Abreu MM, Poh YC, et al. (2020) Conformal coating of stem cell-derived islets for β cell replacement in type 1 diabetes. Stem Cell Reports, 14(1):91–104.
17. Shapiro AMJ, Thompson D, Donner TW, Bellin MD, Hsueh W, et al. (2021) Insulin expression and C-peptide in type 1 diabetes subjects implanted with stem cell-derived pancreatic endoderm cells in an encapsulation device. Cell Rep Med. 2(12):100466.
18. Schulz TC. (2015) Concise review: manufacturing of pancreatic endoderm cells for clinical trials in type 1 diabetes. Stem Cells Trans Med. 4(8):927–31.

19. Ramzy A, Thompson DM, Ward-Hartstonge KA, Ivison S, Cook L, et al. (2021) Implanted pluripotent stem-cell-derived pancreatic endoderm cells secrete glucose-responsive C-peptide in patients with type 1 diabetes. Cell Stem Cell. 28(12):2047–61.
20. Tan WX, Lau HH, Tan NS, Khoo CM, To AKK. (2021) Considerations in using human pluripotent stem cell-derived pancreatic beta cells to treat type 1 diabetes. Recent Adv in iPSCs Ther. 3:173-03.
21. Desai T, Shea LD. (2017). Advances in islet encapsulation technologies. Nat Rev Drug Discov. 16(5):338–50.
22. Cooper-Jones B, Ford C. Islet Cell Replacement Therapy for Insulin-Dependent Diabetes. 2017 Jun 1. In: CADTH Issues in Emerging Health Technologies. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2016-. 157
23. https://clinicaltrials.gov/ct2/show/NCT02239354
24. Dang HP, Chen H, Dargaville TR, Tuch BE. (2022) Cell delivery systems: Toward the next generation of cell therapies for type 1 diabetes. J Cell Mol Med. 26(18):4756–67.
25. https://clinicaltrials.gov/ct2/show/NCT04678557
26. https://www.evaluate.com/vantage/articles/news/deals-snippets/another-diabetes-cell-therapy-deal-vertex
27. . https://crisprtx.com/programs/regenerative-medicine
28. https://diatribe.org/viacyte-and-crispr-introduce-new-stem-cell-therapy-for-type-1-diabetes
29. Philippidis, A. (2022). First patient dosed with VCTX210, a cell therapy for type 1 diabetes. Genet Eng Biotechnol News. 42(5):10-11.
30. https://investors.vrtx.com/news-releases/news-release-details/vertex-announces-positive-day-90-data-first-patient-phase-12
31. https://investors.vrtx.com/news-releases/news-release-details/vertex-presents-new-data-vx-880-phase-12-clinical-trial-american
32. https://investors.vrtx.com/news-releases/news-release-details/vertex-acquire-viacyte-goal-accelerating-its-potentially
33. Spanakis EK, Golden SH. (2013) Race/ethnic difference in diabetes and diabetic complications. Curr Diab Rep. 13(6):814–23.
34. Rajkumar SV. (2020) The High Cost of Insulin in the United States: An Urgent Call to Action. Mayo Clinic Proceedings. 95(1):22–28.