TOURO COLLEGE & UNIVERSITY SYSTEM

The Science Journal of the Lander College of Arts and Sciences

Volume 16
Number 1 *Fall 2022*

50-55

2022

Can Stem Cell Transplantation Restore Insulin Levels in Diabetics?

Nechama Mendelson

Can Stem Cell Transplantation Restore Insulin Levels in Diabetics?

Nechama Mendelson

Nechama Mendelson graduated with a Bachelor of Science degree in Biology in June 2022, and is currently attending Touro University's Physician Assistant program at Central Islip, NY

Abstract

A recent public interest in stem cell research has led to new approaches to treat various pathologies, including diabetes. Diabetes mellitus is characterized by elevated blood glucose levels due to the inability of the β cells in the pancreas to produce insulin. Therefore, the standard diabetes treatment is introducing insulin to the bloodstream. With the advancement of stem cell therapy, a new approach to treating diabetes mellitus is being researched. Scientists are working to differentiate pluripotent stem cells into mature insulin-producing pancreatic beta cells. These cells are then transplanted into in vivo models and observed after a glucose challenge for normal blood glucose and elevated C-peptide levels. The subjects in each study are monitored, and the efficacy of each implantation is evaluated. Scientists have engineered novel retrievable encapsulation devices to prevent an autoimmune attack that can be easily removed in the event of tumor growth. It is evident that there is much potential to stem cell therapy and beta-cell encapsulation as an alternate treatment for diabetes.

Keywords

Diabetes Mellitus
Insulin
β cell
Stem Cell Therapy
C-peptide
Encapsulation Device

Can Stem Cell Transplantation Restore Insulin Levels in Diabetics?

Diabetes mellitus is a chronic health condition defined by hyperglycemia resulting from insufficient or dysfunctional insulin. Insulin is a hormone secreted by beta (β) islet cells in the pancreas in response to blood sugar levels in the body. Diabetes is divided into two categories based on the age of onset and causes. Type I diabetes is an autoimmune disease where the body creates cytotoxic T cells that aim to destroy their pancreatic β cells. These T cells recognize their cells based on their β cell antigens, insulin, and the GAD56 antibody. Type II diabetes is often caused by an unhealthy lifestyle and subsequent progressive β cell dysfunction. Standard care for diabetes requires constant monitoring of blood sugar levels and strict adherence to lifelong insulin injections to keep within the normal range of 80-110 mg dl-1. Though people with diabetes can often live almost normal lives, compliance is exhausting, and negligence in diabetic management can lead to severe complications that may induce blindness, kidney and heart dysfunction, peripheral neuropathies, or premature death (Melton, 2011). Unfortunately, the above plan is only a preemptive method, and cannot replace the highly specific work of the pancreatic β cell. Therefore, replication or restoration of functional β cells and autoimmune prevention is a sought treatment method for diabetes mellitus.

Stem Cells

Stem cell therapy is a potential way to form many cell lineages, and therefore an excellent source for cell replacement therapy, especially for diabetes. Mesenchymal stem cells, or stromal cells, are nonhematopoietic, multipotent cells that are self-renewable. They can be isolated from tissue such as the umbilical cord, liver tissue, adipose tissue, and bone marrow. Mesenchymal stem cells have many advantages that enable scientists to study them and use them for experiments. These cells are easily generated to large masses of cell numbers, can maintain their plasticity, are multilineage, and are anti-inflammatory. They also perform potent secretome functions and contain immunomodulatory properties. (Kotikalapudi et al., 2021) Another advantage is that mesenchymal stem cells are less ethically controversial in comparison to other stem cell types (Lu et al., 2020). Therefore, they are well studied and experimented with to combat tissue degeneration immune-based pathologies such as heart disease, osteogenesis, graft vs. host disease, and Crohn's disease.

Methods

Various databases, including Touro College Online Libraries, JSTOR, and PubMed were used to compile information for this paper. A spectrum of peer-reviewed, original articles on the topics of Diabetes Mellitus, stem cell therapy, islet cell transplantations, and ethics were found, and the relevant data was incorporated into this paper.

Discussion

Formation of Beta Cells

To efficiently study diabetes mellitus, stem cells were generated and used to study the disease on a cellular level, to transplant into mice to create simulated components of the disease as preparation for experiments, and most importantly, to create the functional cells to transplant into human and nonhuman subjects. Methods for cell generation vary, but all techniques follow a basic procedure. Biopsies can be obtained from the skin, liver, pancreatic , embryonic, cadaver, and umbilical cord tissue (Maehr et al., 2009). These cells were differentiated into spheroids, 3D clusters that mimic the dimensions and gradients of signals that are found in early-stage embryonic cells (Fattahi et al., 2021). The cells were then infected with

retroviruses that contain transcription factors such as OCT 4, SOX 2, and KLF4. After which, they were tested for pluripotency markers by confirming the presence of alkaline phosphate activity and reactivity to antibodies against pluripotency markers. Once the pluripotent stem cells resembled human embryonic stem cells, they were analyzed for correct differentiation into the endodermal, mesodermal, and ectodermal germ layers. The last step was to direct differentiation into glucose-responsive insulin-producing cells (Maehr et al., 2009).

Preparation of Host for Experimentation

Experimentation included transplanting stem cells into diabetic subjects and then monitoring and recording each success. Prior to experimentation, scientists prepared animal hosts that would undergo the islet cell transplantation. In many studies, researchers replaced the islet cells of immunocompromised mice with dysfunctional beta cells. Other studies involved the creation of a good host by injecting 180 mg/kg of Sigma (streptozotocin) into nonobese diabetic severe combined immunodeficient male mice (Sapir et al., 2005). Alternatively, some studies were performed based on human experimentation. The subjects in these studies were chosen based on their diabetic history, BMI, and a fasting C-peptide level ≥100 pmol/L (Lu et al., 2020).

C-peptide level was recorded to track the success of each transplantation. C-peptide is produced along with insulin and is responsible for the correct folding and linking of alpha and beta sheets in insulin. Since it is produced at the same rate as insulin and is also released by β cells in equal amounts, C-peptide can be used as a marker for insulin production

Efficacy of Multiple Islet Transplantations

In one experiment, umbilical cords were obtained from reportedly healthy women post-delivery. They were then cut, incubated, cultured, cryopreserved, and tested in a quality control lab. Patients received transfusions of these cells every three months along with dexamethasone injections as prevention. Both the experimental group and control group were given intensive insulin therapy and diabetes education. They were then monitored and followed up with blood tests, standard meal tolerance tests at 3, 6, and 12 months and then yearly. The primary efficacy endpoint was clinical remission of the experimental group participants, as noted by a 10% increase from baseline fasting and postprandial C-peptide level, indicating improved β cell function through the one-year follow-up. At that point, 40.7% of participants in the mesenchymal stem cell treated group kept up clinical remission, which is 2.5 times higher than the control group, who maintained 11% clinical remission on a standard insulin regimen. Even better, two treated participants remained insulin-free within the first three months of introduction and only restarted insulin a little over a year later. Another went 3.8 months without introducing insulin, within six months after the second transplantation. Additionally, almost half of the treated group had increased fasting and postprandial C-peptide levels instead of only 1/5th of the control group. (Lu et al., 2020)

A similar study was performed to test the efficacy of pluripotent stem cell-derived islet cell engraftment on 17 human subjects. These subjects were monitored and given mixed-meal tolerance tests at specific intervals, after which their glucose and C-peptide levels were observed. The test's primary efficacy endpoint was detectable levels of circulating C-peptide after increased blood glucose. Subjects who achieved this were classified as responders, whereas nonresponders had undetectable glucose levels. Explants from the responders showed more significant numbers of graft-derived β cells than non-responders. Additionally, 63% of engrafted cells from subjects highlighted insulin expression, and 35.3% of subjects had positive C-peptide as early as six months post-transplant (Shapiro et al., 2021).

The study led by Sapir et al. suggests the use of liver cells as a possible pancreatic progenitor to create functional insulin-producing cells. First, recombinant adenoviruses were constructed. Then adult and fetal liver tissues were isolated, cut into slices, digested by 0.03% collagenase type I, and cultured. The medium was changed daily. The liver cells were then infected with recombinant adenoviruses and placed under 40 rounds of RT-PCR to denature their genes. The cells were also placed under SF (steroidogenic factor) treatment with PDX-1 until there were normalized human β-actin cDNA. Observations proved that only about half of human liver cells were susceptible to recombinant adenovirus infection, and 20-50% of the PDX-1 expressing cells responded to activation of the insulin promoter.

Insulin secretion of the cells was measured, and the liver cells were then challenged with the introduction of increasing concentrations of glucose and tested for C-peptide reactivity. Mice were prepared as mentioned above, and once the mice's blood glucose levels were measured to be ≥300 mg/dl twice consecutively, the adult liver cells were transplanted into them. After fasting 6 hours, the mice received a glucose injection. Blood was drawn from their tails to monitor C-peptide, mouse insulin, and amylase levels. Results indicate that treated adult human liver cell implantation in the mice caused

a gradual, steady, and significant decline in blood sugar levels that lasted throughout the 60 days of the experiment. Conversely, C-peptide levels increased at the same rate as the drop in blood glucose levels. The normal lives that the mice lived in the 60 days of the experiment and their reversal to hyperglycemia and low C-peptide levels following removal of the cells establish the potential for β cells to be replaced by PDX-1 treated hepatocytes in vivo in the future. This approach is another way to circumvent the ethical issues involved in using fetal or embryonic stem cells to achieve this (Shapiro et al., 2021).

In an experiment to test the capacity of β stem cells to function in vivo and to determine the period length of insulin response post-transplantation between stem cells and pancreatic progenitor cells, the cells were placed under the renal capsules of immunocompromised mice. After a two-week surgical recovery period, both groups of mice were injected with glucose, and after 30 minutes, their serum was collected. In contrast to the pancreatic control progenitor transplanted mice that undergo a 3-4 week maturation phase before producing insulin-secreting islets, 73% of the β-cell transplanted mice showed increased human insulin levels in the bloodstream following a glucose challenge. Even more, two out of six control mice died within eight weeks post-transplantation versus zero out of six β-cell transplanted mice. After at least four months of observation, five out of six control mice died compared to one out of six that received β stem cells, proving that the β cell transplanted mice survive better (Pagliuca et al., 2014).

Multiple studies defend the potential of stem cell therapy. Interestingly, an experiment proved that bone marrow stem cells are insufficient when used alone but were successful when implanted along with mesenchymal stem cells (Urbán et al., 2007). Likewise, scientists experimented to improve the insulin function and survival of islet cells by transplanting them along with adipose tissue-derived stem cells. Adipose tissue- derived stem cells possess anti-inflammatory properties and the potential to revascularize, both of which promoted the grafted cells' survival (Ohmura et al., 2010). Another study was performed over a 50-week course to observe and evaluate the sustainability of device encapsulated stem cells when implanted into non-diabetic immunodeficient mice. Thankfully, all the implants differentiated and the hosts exhibited biologically relevant plasma human C-peptide levels beginning at about five weeks post-transplantation and up to 40 weeks post-transplant, with some animals maintaining normal C-peptide levels beyond that time (Robert et al., 2018).

The Problem and Solution:
Immunoprotective Devices
Cell Encapsulation

Despite the significant success in treating diabetes with β cell transplantation, it is hindered by the need for long-lasting immunosuppression. Immunosuppressive drugs increase infectious disease and malignancy and thereby patient morbidity, but they also cause problems with the regulation of β cell regeneration (Lee et al., 2009). There is also an increased risk of teratoma formation when breeding induced pluripotent cell products (El Khatib et al., 2016). To combat this, new engineering solutions such as cellular encapsulation can almost eliminate the issues above and safely protect against teratoma formation and immune rejection. Scientists engineered an optimal device that allowed for adequate exchange of nutrients and oxygen to sustain the encapsulated cells. It also efficiently transported glucose and insulin to execute the beta cell's purpose. Simultaneously, the capsule inhibited the diffusion of immune cells, antibodies, immunoglobulins, and proinflammatory cytokines from invading. Last, the device was biocompatible and could control potential tumorigenic cells.

Additionally, due to T cells as the primary immune rejector of grafts, the devices must be capable of preventing their activation. Chang and his associates measured the activation of antigen-specific T cells in response to mice with ovalbumin expressing cells encapsulated in nanoporous immunoprotective devices. They first stained the T cell receptor in the transgenic mice before transferring them into wild-type mice. This was done to assess the capability of nanoporous immunoprotective devices in vivo. The cells were then placed into the mice, and their lymph nodes and spleen were removed and checked for growth of ovalbumin-specific cells. Analysis of the dye loss in the unprotected ovalbumin challenge transplant was indicative of T cells being present. The mice with encapsulated cells showed minimal dye loss. This meant that the encapsulated cell transplants can protect against antigen-specific T cells and indicated proliferation for the T cells within the mice.

Both macro and micro encapsulation devices have been invented and studied. Microcapsules are advantageous in maximizing their surface area to volume ratio but have limited control over pore thickness and size, and retrieval, if necessary, has been proven difficult. Alternatively, macrocapsule technology has been more successful. One reason is its capability to be retrieved easily. This is useful in case of an event such as cell escape, reverse differentiation, or teratoma formation where the cells must be immediately removed (Chang et al., 2017).

The macro encapsulation device is a planar pouch of a bilaminar polytetrafluorethylene membrane system. (Others have been designed from polycaprolactone, an FDA approved synthetic fiber (Chang et al., 2017). It is made of long-lasting durable material, and its semipermeable membrane allows for diffusion of nutrients and insulin. Monodisperse alginate beads encapsulate the cells. The even layer is created by a novel microchannel emulsification device (Bitar et al., 2019). This device's implantation in the subcapsular space of the renal compartment or dorsal subcutaneous space is minimally invasive and can be retrieved if needed. Upon testing the device, a few points were noted. When determining the function of encapsulated fetal β cells, the cells were found to have replicated by 3.6%, proving that not only can β cells proliferate within the capsule, they may actually be promoted. Interestingly, adult human islet cells had contrasting results. The C-peptide levels of encapsulated adult cell transplanted animals were only 5% of those of controls one month after transplantation. The results were the same three months post-transplant as well. Further investigation led to the suggestion of cell death of the encapsulated adult β cells. The researchers explored the factors that may have allowed the fetal islet but not the adult islet cells to survive, suggesting differences in ischemic tissue time, growth factors, cytokines, or blood vessels in older and younger tissue (Lee et al., 2009).

Researchers who used an alginate derivative, triazole-thiomorpholine dioxide, as encapsulation material achieved significantly higher levels of human C-peptide in the mice they were studying compared to those in other treatment groups. They saw that 150 days post-transplant encapsulated β cells restored their glucose to normal levels. Again, at 174 days post-transplant, the stem cells still stained positive for human insulin. Additional positive staining for β cell marker Nkx6.1 is proof that the cells maintained their differentiation throughout the experiment (Vegas et al., 2016).

Even with all its benefits, macrocapsules are impaired by their capacity to be packed densely with cells, consequently causing a hypoxic environment for the cells, hindering their insulin secretion (An et al., 2017). Scientists strive to further understand and solve this issue.

Cell Retrieval Devices

β cell encapsulation itself is a tremendous achievement in avoiding long-term immunosuppression. Likewise, approaches in the case of cell retrieval have also been worked upon. An and his colleagues designed a Ca2+ releasing nanoporous polymer thread coated in alginate hydrogel that can be easily retrieved via a minimally invasive laparoscopic surgery. This can be very useful for retrieving and replacing cells that would otherwise be lost in the peritoneal cavity. A thread reinforced alginate fiber for islets encapsulation, named TRAFFIC, was designed with characteristics that enable easy handling, retrieval, and implantation while also being durable. Inspired by spiders' highly adhesive, nonporous silk, the device is made of a rigid polymer thread with a thickness-controlled alginate hydrogel layer. A Ca 2+ releasing mechanism was incorporated into the thread to maintain stem cell regulation. The string was then folded (to limit surface tension that caused the coating to clump) and twisted to create a stable helical structure that resembles a rope. The thread was first placed in the alginate solution, then placed in a Ca/Ba solution to cross-link further. This created the uniform hydrogel layer, which may have infiltrated the porous surface, adding to the thread's adhesion. Then the thread was placed into another alginate-like solution containing cells for encapsulation.

Once created, the engineers dealt with avoiding fibrosis of the thread when placed in the peritoneal cavity and learned that making the thread thicker to 11 mm would prevent this problem. After confirming the mechanical strength, biocompatibility, and transfer property, TRAFFIC was ready to be tested for its potential usage. The device was transplanted laparoscopically into diabetes-induced mice and dogs. The alginate hydrogel layers seemed to be adequate in protecting against xenografts without immunosuppression. This was tested by transplanting both the device with encapsulated cells and naked, unencapsulated cells into mice. As expected, the un-encapsulated cells were quickly rejected by the host mice within two weeks as compared to the islet cells within TRAFFIC that were protected by their hosts (An et al., 2017).

Researchers also studied other factors that can make stem cell therapy more advantageous such as hemocompatibility and immunomodulatory potential. Davies and her colleagues compared the genotypic and phenotypic profiles of stem cell recipients to the bone marrow-derived mesenchymal stem cell donors. They reported that doing so minimized the risk of immune reactions such as rejection and transmission of donor-derived disease or infection (Davies et al., 2016).

Ethical Ramifications to Stem Cell Treatments

Despite all the beneficial effects islet cell transplantation may have, there still are important ethical and safety concerns to consider. One involves choice of cell tissue origin, as embryonic stem cells involve the destruction of a human embryo. With time, new ways to produce pluripotency in mammalian stem cells have been discovered,

avoiding the traditional embryo destruction method. For example, mesenchymal stem cells hold tremendous potential due to their plasticity, differentiation rate, and many places of origin other than embryonic tissue. This discovery has increased the study as a treatment for diabetes and other diseases, but one must keep in mind its tumorous potential (Volarevic et al., 2018).

Conclusion

Beta cell transplantation achieving insulin independence has come a long way. In 1994, only 12.4% of allographs performed resulted in insulin independence for over a week, and only 8.2% for over a year. However, by the year 2000, one research center reported 14.3% insulin independence (Shapiro et al., 2000). In the past decades, the statistics have exponentially increased, with about half of subjects maintaining insulin independence for extended periods in 2020 and 2021. Technology provided tremendous advancement in stem cell research and aided in overcoming safety challenges in transplantation. Islet transplantation's most significant advantage is its elimination of severe hypoglycemia. Several allograft recipients have maintained insulin independence for over 20 years with minimal to moderate exogenous insulin administration(Shapiro et al., 2021). Therefore, stem cell therapy is a promising approach and will hopefully soon fundamentally alter how people with diabetes are treated today (Chang et al., 2017).

References

An, D., Chiu, A., Flanders, J. A., Song, W., Shou, D., Lu, Y.-C., Grunnet, L. G., Winkel, L., Ingvorsen, C., Christophersen, N. S., Fels, J. J., Sand, F. W., Ji, Y., Qi, L., Pardo, Y., Luo, D., Silberstein, M., Fan, J., & Ma, M. (2017). Designing a retrievable and scalable cell encapsulation device for potential treatment of type 1 diabetes. Proceedings of the National Academy of Sciences, 115(2). https://doi.org/10.1073/pnas.1708806115

Bitar, C. M. E., Markwick, K. E., Treľová, D., Kroneková, Z., Pelach, M., Selerier, C. M. O., Dietrich, J., Lacík, I., & Hoesli, C. A. (2019). Development of a microchannel emulsification process for pancreatic beta cell encapsulation. Biotechnology Progress, 35(6). https://doi.org/10.1002/btpr.2851

Chang, R., Faleo, G., Russ, H. A., Parent, A. V., Elledge, S. K., Bernards, D. A., Allen, J. L., Villanueva, K., Hebrok, M., Tang, Q., & Desai, T. A. (2017). Nanoporous immunoprotective device for stem-cell-derived β-cell replacement therapy. ACS Nano, 11(8), 7747–7757. https://doi.org/10.1021/acsnano.7b01239

Davies, L. C., Alm, J. J., Heldring, N., Moll, G., Gavin, C., Batsis, I., Qian, H., Sigvardsson, M., Nilsson, B., Kyllonen, L. E., Salmela, K. T., Carlsson, P.-O., Korsgren, O., & Le Blanc, K. (2016). Type 1 diabetes mellitus donor mesenchymal stromal cells exhibit comparable potency to healthy controls in vitro. Stem Cells Translational Medicine, 5(11), 1485–1495. https://doi.org/10.5966/sctm.2015-0272

El Khatib, M. M., Ohmine, S., Jacobus, E. J., Tonne, J. M., Morsy, S. G., Holditch, S. J., Schreiber, C. A., Uetsuka, K., Fusaki, N., Wigle, D. A., Terzic, A., Kudva, Y. C., & Ikeda, Y. (2016). Tumor-free transplantation of patient-derived induced pluripotent stem cell progeny for customized Islet regeneration. Stem Cells Translational Medicine, 5(5), 694–702. https://doi.org/10.5966/sctm.2015-0017

Fattahi, P., Rahimian, A., Slama, M. Q., Gwon, K., Gonzalez-Suarez, A. M., Wolf, J., Baskaran, H., Duffy, C. D., Stybayeva, G., Peterson, Q. P., & Revzin, A. (2021). Core–shell hydrogel microcapsules enable formation of human pluripotent stem cell spheroids and their cultivation in a stirred bioreactor. Scientific Reports, 11(1). https://doi.org/10.1038/s41598-021-85786-2

Kotikalapudi, N., Sampath, S. J., Sukesh Narayan, S., R., B., Nemani, H., Mungamuri, S. K., & Venkatesan, V. (2021). The promise(s) of mesenchymal stem cell therapy in averting preclinical diabetes: Lessons from in vivo and in vitro model systems. Scientific Reports, 11(1). https://doi.org/10.1038/s41598-021-96121-0

Lee, S.-H., Hao, E., Savinov, A. Y., Geron, I., Strongin, A. Y., & Itkin-Ansari, P. (2009). Human β-cell precursors mature into functional insulin-producing cells in an immunoisolation device: Implications for diabetes cell therapies. Transplantation, 87(7), 983–991. https://doi.org/10.1097/tp.0b013e31819c86ea

Lu, J., Shen, S., Ling, Q., Zhang, W., Qu, D., Wang, B., Bi, Y., & Zhu, D. (2020). One repeated transplantation of allogeneic umbilical cord mesenchymal stromal cells in type 1 diabetes: An open parallel controlled clinical study. https://doi.org/10.21203/rs.3.rs-115774/v1

Maehr, R., Chen, S., Snitow, M., Ludwig, T., Yagasaki, L., Goland, R., Leibel, R. L., & Melton, D. A. (2009). Generation of pluripotent stem cells from patients with type 1 diabetes. Proceedings of the National Academy of Sciences, 106(37), 15768–15773. https://doi.org/10.1073/pnas.0906894106

Melton, D. A. (2011). Using stem cells to study and possibly treat type 1 diabetes. Philosophical Transactions of the Royal Society B: Biological Sciences, 366(1575),

2307–2311. https://doi.org/10.1098/rstb.2011.0019

Ohmura, Y., Tanemura, M., Kawaguchi, N., Machida, T., Tanida, T., Deguchi, T., Wada, H., Kobayashi, S., Marubashi, S., Eguchi, H., Takeda, Y., Matsuura, N., Ito, T., Nagano, H., Doki, Y., & Mori, M. (2010). Combined transplantation of pancreatic islets and adipose tissue-derived stem cells enhances the survival and insulin function of islet grafts in diabetic mice. Transplantation, 90(12), 1366–1373. https://doi.org/10.1097/tp.0b013e3181ffba31

Pagliuca, F.W., Millman, J. R., Gürtler, M., Segel, M., Van Dervort, A., Ryu, J. H., Peterson, Q. P., Greiner, D., & Melton, D. A. (2014). Generation of functional human pancreatic β cells in vitro. Cell, 159(2), 428–439. https://doi.org/10.1016/j.cell.2014.09.040

Robert, T., De Mesmaeker, I., Stangé, G. M., Suenens, K. G., Ling, Z., Kroon, E. J., & Pipeleers, D. G. (2018). Functional beta cell mass from device-encapsulated hesc-derived pancreatic endoderm achieving metabolic control. Stem Cell Reports, 10(3), 739–750. https://doi.org/10.1016/j.stemcr.2018.01.040

Sapir, T., Shternhall, K., Meivar-Levy, I., Blumenfeld, T., Cohen, H., Skutelsky, E., Eventov-Friedman, S., Barshack, I., Goldberg, I., Pri-Chen, S., Ben-Dor, L., Polak-Charcon, S., Karasik, A., Shimon, I., Mor, E., & Ferber, S. (2005). Cell-replacement therapy for diabetes: Generating functional insulin-producing tissue from adult human liver cells. Proceedings of the National Academy of Sciences, 102(22), 7964–7969. https://doi.org/10.1073/pnas.0405277102

Shapiro, A. M. J., Lakey, J. R. T., Ryan, E. A., Korbutt, G. S., Toth, E., Warnock, G. L., Kneteman, N. M., & Rajotte, R. V. (2000). Islet transplantation in seven patients with type 1 diabetes mellitus using a glucocorticoid-free immunosuppressive regimen. New England Journal of Medicine, 343(4), 230–238. https://doi.org/10.1056/nejm200007273430401

Shapiro, A. M. J., Thompson, D., Donner, T. W., Bellin, M. D., Hsueh, W., Pettus, J., Wilensky, J., Daniels, M., Wang, R. M., Brandon, E. P., Jaiman, M. S., Kroon, E. J., D'Amour, K. A., & Foyt, H. L. (2021). Insulin expression and C-peptide in type 1 diabetes subjects implanted with stem cell-derived pancreatic endoderm cells in an encapsulation device. Cell Reports Medicine, 2(12), 100466. https://doi.org/10.1016/j.xcrm.2021.100466

Urbán, V. S., Kiss, J., Kovács, J., Gócza, E., Vas, V., Monostori, É., & Uher, F. (2007). Mesenchymal stem cells cooperate with bone marrow cells in therapy of diabetes. Stem Cells, 26(1), 244–253. https://doi.org/10.1634/stemcells.2007-0267

Vegas, A. J., Veiseh, O., G, M., Millman, J. R., Pagliuca, F. W., Bader, A. R., Doloff, J. C., Li, J., Chen, M., Olejnik, K., Tam, H. H., Jhunjhunwala, S., Langan, E., Aresta-Dasilva, S., Gandham, S., McGarrigle, J. J., Bochenek, M. A., Hollister-Lock, J., Oberholzer, J., … Anderson, D. G. (2016). Erratum: Corrigendum: Long-term glycemic control using polymer-encapsulated human stem cell–derived beta cells in immune-competent mice. Nature Medicine, 22(4), 446–446. https://doi.org/10.1038/nm0416-446e

Volarevic, V., Markovic, B. S., Gazdic, M., Volarevic, A., Jovicic, N., Arsenijevic, N., Armstrong, L., Djonov, V., Lako, M., & Stojkovic, M. (2018). Ethical and safety issues of stem cell-based therapy. International Journal of Medical Sciences, 15(1), 36–45. https://doi.org/10.7150/ijms.21666