Review Article

Advances in Curing Type 1 Diabetes: Stem Cell Therapy, Bioprinting, and Islet Transplantation

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ABSTRACT

Background and Objectives: Characterized by insulin insufficiency due to irreversible pancreas defects, type 1 diabetes is traditionally managed by regular insulin supplementation. Recently, tissue regenerative technology coupled with advanced-level surgical intervention has created hope for a cure. Research in this direction started with replacing defective pancreas with healthy ones. However, the strategy met showed limited success. Presently, extensive work is being conducted to replace the damaged β cells with healthy ones and create insulin-producing cells from stem cells. This study reviews various research strategies used to replace or regenerate β cells for curing diabetes.

Methods: The literature survey was done on PubMed and Google Scholar until June 2023. The keywords used were "type 1 diabetes," "cure," "techniques," "islet transplantation," "encapsulation of β cells," and "stem cells," etc. Full-length research and review articles were used as the basis for the preparation of the manuscript. Papers describing the basic features and rationale supporting the development of technologies were included, whereas clinical aspects and case studies were excluded.

Results: Mainly, three important approaches were discussed. Treatment involves transplantation of whole organ (pancreas), islet, and stem cells derived β progenitor cells. A brief discussion was included for each technique, such as the extraction of β cells and generation of insulin-producing cells from stem cells, along with the essential findings obtained from each approach.

Conclusion: The review demonstrated various strategies researchers have undertaken to find a cure for type 1 diabetes in terms of insulin independence.

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Introduction

Diabetes has been recognized as an illness by ancient Egyptian and Indian physicians who identified the disease as "too great emptying of urine." The ancient Indian physicians Charak and Sushruta described different symptoms of the disease, which were later classified as type I and type II diabetes [1]; However, its course and cure were not sufficiently investigated. Considering the level of scientific knowledge of that period, this issue was somewhat expected. In the past few decades, the world has seen an explosion in diabetes and its related serious complications [2-4]. Regarding mortality, diabetes occupies a position in the top 10 diseases. This resulted in concerted attempts to cure diabetes.

Since 2000, the International Diabetes Federation has been reporting the regional and global occurrence of diabetes. As per their report, the disease is progressing almost exponentially. In 2019, approximately 463 million people suffered from the disease, which had grown to 537 million adults by 2021 [5]. The number is projected to reach 643 million by 2030 and 783 million by 2045 [6]. Of the two types, type 1 diabetes is considered an incurable disease and is managed by insulin supplementation. In addition to the pain and anxiety, the treatment is financially challenging as well. In 2017, global health expenditure due to diabetes treatment was estimated at USD 727 billion and is projected to reach USD 825 billion by 2030 [7].

In the absence of a cure, exogenous insulin treatment has remained a mainstay in treating severe cases. Still, it can result in episodes of hyperglycemia and hypoglycemia if not monitored religiously [8].

Of late, the focus of diabetes research has shifted from management to cure. With the advent of tissue regenerative technologies, there is a new hope to replace the damaged β cells with healthy ones to receive a cure. This review gives an overview of various research strategies used to replace or regenerate β cells for curing diabetes.

Strategies used for β cell supplementation

Transplantation of the whole organ

The effort to cure type 1 diabetes through transplantation of the whole pancreas started quite early. The first attempt to cure diabetes by grafting pancreatic tissue into the human body was made by Dr. Watson Williams in 1893. Dr. Willams grafted three fragments of sheep pancreas into the subcutaneous tissue of a 15-year-old diabetic patient [9]. This study aims to reestablish normoglycemia by replenishing the depleted pancreatic islets [10]. The first attempt to replace diseased pancreas with healthy human tissue (duct ligated segmental pancreas) was made in 1966 at the University of Minnesota, Minneapolis [11, 12]. The procedure was investigated and modified for the next two decades to increase efficiency.

Pancreas transplantation, using allogeneic organs procured from deceased multi-organ donors, was a surgical procedure that was met with success [13]. However, not every diabetic patient could withstand the rigors of this procedure. Patients who have type 1 diabetes along with healthy and free of secondary complications (body mass index [BMI] <30 kg/m^2) were considered suitable for the procedure [14]. The legal procedure and the availability of matching donors was a constraint. There was some inherent difficulty associated with the process. In addition to the common risk of major surgery, there was a need for long-term immunosuppression [15]. Moreover, the risk of death due to the failure of the process was relatively high when the pancreas was transplanted alone. As the pancreas shares blood supply with other organs (liver and pancreas), simultaneous transplantation of both organs lowered the risk significantly [16].

However, the progress was less than satisfactory when long-term survival was considered. The graft loss within the first 90 days of the transplantation was one significant difficulty with the procedure. Although the rejection rate declined from 14% in 1999 to 8.2% in 2014, rather than the whole pancreas, grafting a cluster of insulin-producing cells would be a better alternative [17].

β cell transplantation

In humans, insulin is produced in the pancreatic islet, which houses mainly three types of cells (α, β, γ). Of these, only β cells produce insulin while α cell releases glucagon, which helps convert glycogen to free glucose to counteract hypoglycemia. Each islet carries approximately 1560±20 cells, most of which are β-cells (1140±15) [18]. Volume-wise, islet occupies only 2% of the whole pancreas, and supplying nutrition to this small volume of cells is considered far more convenient than supporting the entire pancreas. An experiment by Lacy and Cols in 1972 brought the idea to the forefront [19]. The researchers transplanted the diabetic rodents with pancreatic islets and successfully reversed the hyperglycemia. Henceforth, the focus for curing type 1 diabetes was directed to autologous islet transplantation [20]. The

procedure came with an added advantage. There was no restriction for placing the islet close to its normal position in the body. Any body area with a good nutrient and oxygen supply could be used to support the insulin-producing cells. However, separating the islets from the whole pancreas is time-consuming and laborious [21].

The challenges and the following issues needed consideration to make the treatment successful.

Donors

Although the transplantation of healthy β cells is the perfect fix for treating severe type 1 diabetes, the process is highly complicated. For insulin-independent survival, greater than 5000 islets/kg of body weight should be grafted in a human [22]. The availability of the right kind of islet is a challenge, and often, allogenic transplantation is the only way to supply the need. The introduction of the Edmonton protocol brought hope as the pancreas extracted from diseased people could be used as transplants [23]. However, the shortage of pancreas and the legalities involved with the deceased donors remain one of the bottlenecks. The problem gets multiplied by the low extraction yield of islets as well. A sizeable fraction of islets are lost during the process (extraction and intraportal islet infusion) [22].

Harvesting

In the extraction phase, tissue is cut into small pieces using surgical scissors, and cells are extracted by collagenase treatment. Within the islets, most cells are β cells; however, they also stay in association with other cells. In reality, recipients receive a large volume of islets (11000 islet equivalents per kg of the body weight) extracted from two or more donors for successful transplantation [24]. Meanwhile, β cells start dying fast once the blood circulation stops. This translates to a greater demand for islets and an increased risk of graft dysfunction [25].

Transplantation

In the sequence of events, the actual transplantation is the least difficult. The purified β cells are slowly infused into the portal vein of patients through a catheter. The cells settle in the liver. With its rich nutrient and oxygen supply, the liver plays home to the β cells that produce insulin to affect normoglycemia. However, the real challenge comes after the transplantation.

Protecting the transplanted cells

In the human body, β-cell development occurs during the first trimester of pregnancy. The proliferation of β cells continues in the postnatal period as well; however, the rate of cell mitosis declines progressively. A stable state is reached in the second year of life [26]. After transplantation, islet functions are gradually lost for various reasons, such as the quality of islets used and the alloimmune response [27]. Several strategies have been tried to protect and keep the transplanted beta cells functional.

Immunosuppression

Transplanted β cells are a target for allograft rejection, and in the absence of immunosuppression, they cannot survive long. Lymphocytes infiltrate the allogeneic islets, leading to islet-specific antibody production, making using immunosuppressants necessary [28, 29]. In type 1 diabetes, β cells are mainly attacked by T cells, and immunosuppressive agents prevent T-cell clonal expansion.

Immunosuppression can be done in various ways. Two crucial mechanisms by which these agents work include T-cell and B-cell targeting therapy. Therapeutic agents that target T cell function can be broadly categorized based on two types of signals they inhibit. Drugs like cyclosporine and tacrolimus are calcineurin inhibitors (signal 1). They disrupt the calcineurin-dependent signaling pathway, leading to initial T cell gene transcription necessary for additional activation. On the other hand, abatacept and belatacept are signal two targeting agents. Rituximab, ocrelizumab, ofatumumab, and veltuzumab are the agents that target the B-cell. The goals of B cell inhibition include inhibiting the humoral response to auto- or alloantigen, antigen presenting cell function, and B/T cell interactions that lead to efficient T cell activation and proliferation. Immunosuppressive therapy comes with several side effects. Some of calcineurin inhibitors' most common side effects are nephrotoxicity, electrolyte disturbances (hyperkalemia and hypomagnesemia), hypertension, and neurotoxicity (manifesting as tremor or headache). Signal 2 inhibitors cause headache, nausea, or cold symptoms, such as stuffy head or nose tic. Pain, irritation, or swelling at or near the injection site are common occurrences with both types. Sometimes, the side effects are more harmful than the disease they aim to cure [30].

Creating a barrier around the β cells

Physical separation was the second strategy to protect the β cells from immune attack. If the islets could be covered with a semipermeable film, it might initially obstruct the recognition process and stop the cascade of immunological events. In such cases, immune suppressants will not be needed. The idea soon caught up with the researchers and developed into a major field in beta cell transplantation research [31]. Normally, cells produce proteins, approximately 50% of which get converted into particulate insulin. Once formed, this very particle takes part in regulating β cell activities [32].

Wrapping of β cells within a membrane imposes additional demand on the system. The membrane should be inert and compatible with its capsulated contents to prevent immune rejection. It should be able to maintain its physical integrity and provide a smooth surface so that protein and cell attachment is prevented [33]. Finally, there is a need to develop blood vessels around the encapsulated islets to ensure cell survival immediately after the process of transplantation [32].

Hydrogel-coated β cells

Hydrogels are networks of polymeric materials that, because of their structure, can imbibe high quantities of water but do not dissolve in it [30]. Due to their similarity with the extracellular environment, they provide a friendly atmosphere for the cells to survive and grow [34]. Many factors must be considered for creating a coating membrane around the β islets. First, in addition to being biocompatible, it should be able to create a physical barrier to conceal the surface of transplanted cells. Secondly, it should allow the passage of nutrients and oxygen but prevent cytotoxic substances from accessing the cell [30]. Few materials can fulfill this demand (for instance, the hydrogel can satisfy this demand). In short, the membrane should be semi-permeable, selectively allowing only the nutrients inside and the end products of metabolism of the islet cell outside. This property highly depends on the membrane's pore size, thickness, and rigidity. Any foreign body would attract anti-inflammatory cells [35], which can induce graft rejection through the local anti-inflammatory reaction. The attachment of the inflammatory cells around the membrane may result in an impermeable fibrotic capsule, starving the inner resident cells of oxygen and nutrients [36, 37]. Therefore, the selection of membrane material is a crucial factor for the survival of the graft.

Both natural (alginate, chitosan, agarose, fibrin) and synthetic polyethylene glycol (PEG) hydrogels are used for islet encapsulation [37]. Researchers especially consider PEG favorable as they show better tunability than the natural types in terms of porosity, stability, biocompatibility, and mechanical strength. The mechanical properties of the PEG-based hydrogels can be tuned by altering concentration and molecular weight. The stiffness of hydrogel is an essential criterion in islet transplantation as soft gels cause less anti-inflammatory reaction compared to stiffer gels. At a concentration level of 5% to 10%, PEG generates a soft hydrogel [38].

Cell survival was also affected by the chemical composition of the encapsulating material. Islets coated with polyethylene di-acrylate, when embedded in a complex hydrogel of thio-glycosaminoglycan, thiogelatin, and thioheparin, could maintain the structure and function of islets and improve the formation of blood vessels. Co-encapsulation of immunomodulators has also been investigated [32].

Capsules containing PEG on the surface are also shown to reduce the secretion of interleukin-2 – a cytokine produced by the T lymphocytes. IL-2 affects graft rejection by supporting other T and B lymphocytes' growth and activity [32].

Because of the apparent advantages of the encapsulation technique, in-depth research has been done on this aspect. Encapsulation of the β cells by hydrogel can be done in many ways, which include: A) Nanoencapsulation, by placing thin hydrogel films around individual islets, B) Microencapsulation of small groups of islets, individual islets, or other insulin-producing cells within spherically shaped hydrogel microcapsules, C) Macroencapsulation of islets or other insulin-producing cells within bulk hydrogels that can be shaped and molded within encapsulating devices [39].

Though islet encapsulation is a great technique to isolate the β cells from physical interaction with the immune system, the method has several difficulties. Too many factors need to be controlled in this method. The nature of the polymer that makes the membrane, its pore size, and its thickness affect the mass exchange between the cells and their environment. Often, cell survival is reduced by hypoxia and insufficient nutrients. PEG-based hydrogels suffer from the drawback of being hydrolytically degradable [30], and the protection offered by the polymeric membrane is limited by its degradation time. With time, hydrogels the encapsulating media, degrade, and islets are exposed to the immune attack. The process

Table 1. List of completed/active clinical trials on mesenchymal stem cells in t1dm

S. No	Trial ID	Study start date	Sponsors	Status	Phase	Official title	Purpose	Biological intervention	Location
1	NCT01068951	01-06-2010	Uppsala University Hospital	Completed	NA	Open study to evaluate the safety and efficacy of autologous mesenchymal fi stem cells in treatment of recently diagnosed patients with type 1 diabetes mellitus	To test if the development of autoimmune diabetes may be halted by the immune modulatory properties of mesenchymal stem cells	Mesenchymal stem cells	Sweden
2	NCT03920397	01-03-2015	Universidade Federal do Rio de Janeiro	Completed	NA	Allogenic adipose derived mesenchymal stem cells and vitamin d supplementation in patients with recent-onset type 1 diabetes mellitus	Unspecified	Infusion of adipose tissue-derived stem/stromal cells and oral Cholecalciferol supplementation	Rio de Janeiro, Brazil
3	NCT04078308	06-07-2015	Royan Institute. Tehran University of Medical Sciences, Iranian Stem Cell Council	Unknown	Phase 1, Phase 2	Phase I/II clinical trial to examine the safety and efficacy of transplantation of fi Mesenchymal stem cells in new-onset type 1 diabetes patients	Modulate immune response and improve	Intravenous Injection of autologous mesenchymal stem cells,Other: Intravenous injection of placebo	
4	NCT02940418	19-02-2017	Sophia Al-Adwan	Unknown	Phase 1	The use of mesenchymal stromal cells (MSC) in type 1 diabetes mellitus in adult humans: Phase i clinical trial	Unspecified	Adipose mesenchymal cells with bone marrow mononuclear cells	Cell therapy center, Amman, 11942, Jordan
6	NCT03912480	05-01-2019	CAR-T (Shanghai) Biotechnology Co., Ltd.	Unknown	Early phase 1	Study on the efficacy and safety of stem fi cells from human exfoliated teeth in treating diabetic patients with significantly reduced islet	To evaluate the safety and efficacy of Stem cells from human exfoliated teeth transplantation in patients with reduced islet function	Stem cells from human exfoliated teeth	Changhai hospital, Shanghai, China
7	NCT03973827	17-05-2019	NextCell Pharma Ab	Active/Recruiting	Phase 1, Phase 2	An open label, parallel single center trial of Wharton's jelly derived allogeneic mesenchymal stromal cells repeatedly treated to preserve endogenous insulin production in adult patients diagnosed with type 1 diabetes	To investigate safety and tolerance after a repeated allogeneic infusion of WJMSCs intravenously after one year following the repeated treatment.	Drug: ProTrans, placebo	Huddinge, Sweden
8	NCT04061746		Medical University of South Carolina. National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK	Recruiting	Phase 1	Cellular therapy for type 1 diabetes using mesenchymal stem cell	To determine efficacy of allogeneic umbilical fi cord-derived mesenchymal stromal cells for the treatment of new-onset T1D and to understand the mechanisms of protection	Biological: Mesenchymal stem cells (MSCs);Other: Placebo infusion (plasmalyte A with 0.5% human serum albumin	South Carolina, United States
9	NCT02893306	2012-03	Universidad del Desarrollo	Unknown	Phase 2	MSC administration for the management of type 1 diabetic patients	To evaluate whether the administration of multipotent stromal cell also referred as to mesenchymal stem cells (MSCs), modified type 1 diabetes progression.	MSCs	Clinica Alemana de Santiago, Santiago, Region Metropolitana, Chile

S. No	Trial ID	Study start date	Sponsors	Status	Phase	Official title	Purpose	Biological intervention	Location
10	NCT01322789	2008-09	University of Sao Paulo	Unknown	Phase 1, Phase 2	Safety and efficacy of mesenchymal stem cells in newly-diagnosed type 1 diabetic patients	To determine the safety and efficacy of intravenous infusions of mesenchymal stem cells in newly diagnosed type 1 diabetic patients.	Intravenous mesenchymal stem cell infusion	SÃ£o Paulo, Brazil
11	NCT01374854	2009-01	Fuzhou General Hospital	Unknown	Phase 1, Phase 2	Umbilical mesenchymal stem cells and mononuclear cells infusion in type 1 diabetes mellitus	To prove the hypothesis that infusion of USC-MSCs may n re-differentiate into local tissues in diabetes mellitus patients, resulting in improvement of diabetic control	Umbilical mesenchymal stem cell (UC-MSCs) infusion| DRUG: Traditional therapy	Fuzhou, Fujian, China
12	NCT01219465	2010-09	Qingdao University	Unknown	Phase 1, Phase 2	Umbilical cord mesenchymal stem cells infusion for initial type 1 diabetes mellitus	To determine whether umbilical cord Mesenchymal Stem Cells of treatment for initial type 1 diabetes is safe and effective.	Umbilical cord mesenchymal stem cells	Qingdao, Shandong, China
13	NCT00646724	2008-01	Fuzhou General Hospital	Unknown	Phase 1, Phase 2	Cotransplantation of islet and mesenchymal stem cell in type 1 diabetic patients	To evaluate the safety and efficacy of Cotransplantation of Islet and Mesenchymal Stem Cell in Type 1 Diabetic Patients.	Cotransplantation of islet and mesenchymal stem cell	Fuzhou, Fujian, China
14	NCT03484741	01-04-2017	Van Hanh General Hospital	Unknown	Phase 1, Phase 2	Mesenchymal Stem Cell Therapy for Type 1 Diabetes Mellitus Patients	To evaluate the safety and efficacy of mesenchymal stem cells (MSCs) transplantation for type 1 Diabetes Mellitus patients.	MSC and PRP	Ho Chi Minh, Vietnam
15	NCT01143168	2010-08	Cellonis Biotechnology Co. Ltd.	Unknown	Phase 1, Phase 2	Stem cell therapy for type 1 diabetes mellitus	To evaluate the feasibility, efficacy, and safety of transplantation therapy using bone marrow mononuclear cells and umbilical cord mesenchymal stem cells for patients with type 1 diabetes mellitus	Autologous bone marrow mononuclear cells and umbilical cord mesenchymal stem cells	P. R. China, Beijing, China
16	NCT05308836	04-10-2021	Vinmec Research Institute of Stem Cell and Gene Technology	Unknown	Phase 1	Evaluate safety of adipose derived mesenchymal stem cell transplantation for type 1 diabetes treatment	To evaluate the safety of intravenously (IV) administered adipose-derived mesenchymal stem cell (AD-MSC) in patients with type 1 diabetes mellitus (T1D)	Adipose-derived mesenchymal stem cell	Hanoi, Vietnam
17	NCT01496339	2012-01	S-Evans Biosciences Co., Ltd.	Unknown	Phase 1, Phase 2	Human menstrual blood-derived mesenchymal stem cells transplantation in treating type 1 diabetic patients	To investigate whether the treatment of human menstrual blood-derived mesenchymal stem cells which would be applied to diabetes patients is safe and effective.	MSCs transplantation |DRUG: Exogenous insulin injection daily	Thangzhou, Zhejiang, 310003, China

S. No	Trial ID	Study start date	Sponsors	Status	Phase	Official title	Purpose	Biological intervention	Location
18	NCT01686139	2016-03	Sheba Medical Center	Unknown	Phase 1	Safety study of stem cells treatment in diabetic foot ulcers	To determine the safety and efficacy of cultured Bone Marrow Mesenchymal Stromal Cells (BM-MSCs) from allogeneic donors for the treatment of chronic leg wounds of diabetic patients.	ABMD-MSC	Ramat Gan, Israel
19	NCT04869761	07-10-2021	LaTonya J. Hickson	Recruiting	Phase 1	Stem Cell Therapy For Chronic Kidney Disease	To assess the safety and tolerability of allogeneic mesenchymal stem / stromal cell therapy in individuals with chronic kidney disease.	DRUG: Allogeneic adipose-derived mesenchymal stem cells (MSC)-Single Infusion-Two Infusions	Jacksonville, Florida, Rochester Minnesota, United States
20	NCT02138331	2014-04	General Committee of Teaching Hospitals and Institutes, Egypt	Unknown	Phase 2, Phase 3	Effect of microvesicles and exosomes therapy on β^2-cell mass in type i diabetes mellitus (T1DM)	To check the hypothesis that intravenous infusion of cell-free umbilical cord-blood derived MSC microvesicles may reduce the inflammatory state and hence improve the β^2-cell mass as well as the glycemic control of the patients of T1DM.	MSC exosomes.	Cairo, Egypt|
21	NCT00690066	11-06-2008	Mesoblast, Inc.	Completed	Phase 2	Prochymal® (human adult stem cells) for the treatment of recently diagnosed type 1 diabetes mellitus (T1DM)	To establish the safety and efficacy of multiple administrations of PROCHYMAL® in participants recently diagnosed with type 1 diabetes mellitus.	DRUG: PROCHYMAL® | DRUG: Placebo	United States
22	NCT05207995	01-03-2022	Institute of Biophysics and Cell Engineering of the National Academy of Sciences of Belarus	Not yet recruiting	Phase 1, Phase 2	The treatment of patients with type 1 diabetes mellitus with autologous tolerogenic dendritic cells	To determine the safety and tolerability of the administration of tolerogenic dendritic cells in patients with type 1 diabetes mellitus.	Autologous tolerogenic dendritic cells|OTHER: Standard treatment according to the clinical protocols	Belarus
23	NCT01157403	2010-07	Lu Debin	Unknown	Phase 2, Phase 3	Autologous transplantation of mesenchymal stem cells for treatment of patients with onset of type 1 diabetes	To study the safety and efficacy of autologous bone marrow mesenchymal stem cells in the treatment of newly diagnosed patients with T1DM.	Autologous transplantation	Chongqing, 400038, China

S. No	Trial ID	Study start date	Sponsors	Status	Phase	Official title	Purpose	Biological intervention	Location
24	NCT02763423	2009-01	The Affiliated Nanjing Drum Tower Hospital of Nanjing University Medical School	Unknown	Phase 2	Allogeneic umbilical cord mesenchymal stem cell transplantation for type 1 diabetes with diabetic ketoacidosis	Phase II trial: To determine whether allogeneic umbilical cord mesenchymal stem cell transplantation is effective in the treatment of patients with severe type 1 diabetes.	Umbilical cord mesenchymal stem cell	Jiangsu, China
Studies that were withdrawn and terminated were excluded*									

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is slow and fails to provide permanent insulin independence. Currently, several clinical trials are going on to assess the success of this technique. Table 1 mentions some of the important studies [40].

3D bioprinting

3D bioprinting is a novel technology that can construct any tissue starting from scratch. To keep the cells alive and functional, they are suspended in a matrix that resembles the natural matrix of the body. Since hydrogels resemble the body matrix in many ways, cells are usually suspended in hydrogels. The combination of cell and hydrogel is known as bioink. In this technique, bioink is laid layer by layer on a surface to create 3-dimensional shapes. Polymers are the backbone of hydrogels, and natural polymers, because of their excellent cytocompatibility, are preferred in making the bioink. As the medium is aqueous, substances required for cell growth (growth factor and other bioactive agents) can be co-administered. For ease of spraying, the material should be fluid; however, the fluidity must be reduced once sprayed. Without solidification, the shape cannot be retained. The conversion of the bioink from a fluid to a solid can be done in several ways. The exact mechanism depends upon the nature of the hydrogel medium. It is often done using bioinks with cross-linking agents dissolved in them.

Mechanism-wise, bioprinting has evolved into four major types as follows: Extrusion-based, inkjet-based, stereo-lithography-based, and laser-energy-driven. Solid structures can be created by using the VAT polymerization technique. Accordingly, a polymeric bioink (photopolymer) containing live cells is deposited layer by layer on a predetermined design. As this arrangement is exposed to light of appropriate frequency, the resin solidifies or cures into the desired shape. Figure 1 depicts different bioprinting approaches for creating pancreatic constructs [41]. In all forms, bioink is deposited by gentle force at a specific design generated by a computer. The deposition is done through a nozzle or as a mist in a controlled manner. Though the technique has created much hype, the concept's commercial viability is faced with several challenges. Both cell survival and

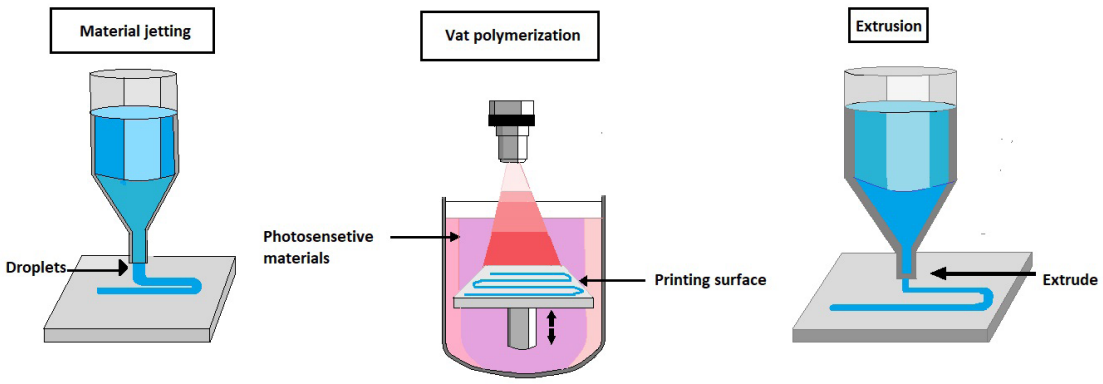

Figure 1. Different bioprinting approaches for creating pancreatic constructs

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functionality are affected by the stress imposed by the printing process. For example, in inkjet- and extrusion-based bioprinting, cells are subjected to considerable shear stress during ejection. In laser-driven and stereolithography-based bioprinting, cells endure thermal and radiative stress. Cell viability is also affected by changes in temperature rheological properties of hydrogels. This stress often results in cell shrinkage and condensation of nuclei, which compromise their functionality even if they survive.

The attempt to create a bioartificial pancreas by 3D printing technology was first reported by Professor Wang in 2009 [42]. In a medium of natural hydrogels, Professor Wang had embedded adipose stem cells. When these embedded cells and islets were printed on the live organs of similar physiological characteristics, adipose stem cells differentiated into vascular stem cells and adipocytes. When different drugs challenged the system, they showed the standard physiological response.

The work was a significant contribution to the development of strategies to cure type 1 diabetes. Later, another group of researchers encapsulated the islets into alginate/methyl cellulose hydrogels and formed a 3D structure by bio-printing. Within the hydrogel covering, islets functioned efficiently to produce insulin and glucagon [43]. For efficient printing, bioink should have good flowability. A research group on this aspect produced new media for bioink by incorporating Pluronic F127 and hypomethylated pectin into the alginate solution. Pluronic F 127 is a polymeric surfactant from ethylene and polypropylene. Aqueous Pluronic F 127 solutions are plastic and have a high yield stress value [44, 45]. The process of bioprinting imposes significant stress on the cells.

Creating insulin-producing cells from stem cells

Attention has recently been drawn to producing insulin-secreting cells by differentiating stem cells. Stem cells obtained from various sites are being studied. Stem cells from the umbilical cord are highly efficient in differentiating into insulin-producing cells. Perhaps the most promising source of beta cells is the inner cell mass of blastocysts of human embryos [46]. Extensive research is being conducted to produce β and β progenitor cells from mesenchymal stem cells (MSC) [47]. MSC cells release immunomodulatory molecules, which can prevent β-cell destruction [48]. However, removing the stem cells from live donors is a big hurdle. A renewable source of the same could be deceased donors, though the process is elaborate [49].

Isolation of mesenchymal stem cells

Rao et al [49] described a method for the preparation of beta cells using mesenchymal stem cells of deceased donors. Adipose tissue obtained from the abdomen was minced into pieces and suspended in 0.9% saline, which was filtered through a series of bags (AC: Px) and centrifuged to obtain vascular stromal fraction. The cell pellet contained MSCs and other cell types identified through phenotyping by flow cytometric analysis.

Expansion of mesenchymal stem cells

Cells (after proper counting) were added to the conditioned cell culture flask using special media that supported the growth of MSC. Once 80% confluency was obtained, they were removed by trypsinization procedure for further passaging. MSCs are made to differentiate into β cells through the following three-step process.

Pancreatic cells have their origin in the endodermal germ layer. Hence, the first stage in converting MSCs to β progenitor cells is the formation of definitive endoderm- a transient phase in which an epidermal layer is created. MSCs and other growth factors are grown for two days in serum-free DMEM/F12.

In the second phase, the cells are suitably diluted to a desired cell concentration in CTS $^{(TM)}$ media and added to culture plates. A complete growth media (DMEM/F12) is added as the cells settle down at the surface. In this phase, cells are induced to differentiate into pancreatic endoderm using another special medium. The duration of this stage is approximately two days.

MSCs are finally converted to β cells in the third stage using a glucagon-like peptide -1, containing growth media. Glucagon-like peptide -1 promotes β-cell survival [50]. The conversion to β cells is confirmed by immunohistochemistry.

ViaCyte, a San Diego based company, is much in the news for developing two products, PEC direct and PEC encap, which can potentially mimic the pattern of real-time blood glucose level regulation. Both systems use stem cells to regenerate pancreatic islet progenitor cells known as PEC-01™ cells. In humans with functional pancreas, the glucose level is maintained at a physiologically normal level mainly by both α and β cells. The PEC-01™ cells can differentiate into β and α cells and are especially recommended for type 1 diabetic patients suffering from frequent hypoglycemia. In the PEC direct system, the cells are enclosed in a perforated pouch,

which allows direct vascularisation. In contrast, the PEC encap has a membrane wrapping around it to protect the progenitor cells from the recipient's immune system to minimize the need for immunosuppression. 2014, they got Food and Drug Administration (FDA) approval for conducting clinical trials. The results of the test were mixed. The cell survival was prolonged up to 24 months but highly variable among subjects. Foreign body reaction to the device components is suspected to be the cause [51]. Figure 2 explains the development method of the PEC-Encap device created by ViaCyte.

Conclusion

Curing type 1 diabetes by replacing the insulin-deficient pancreas with a healthy one is not a new idea. The first transplantation occurred as early as 1966, and the process was met with reasonable success. The chief advantage associated with this method was that insulin-producing islet cells were present in their natural environment. According to the international pancreas transplant registry reports, over 67000 transplants have been performed globally; however, the major disadvantage associated with this procedure is invasiveness and strong immunogenicity. Moreover, the demand for the pancreas outnumbers supply. The majority of pancreas grafts are retrieved from brain-dead donors whose pancreatic cells are still alive. The process is subjected to strict legal procedures and narrow acceptance criteria (BMI, age, lifestyle factors). Regardless of these constraints, it is the best short and long-term treatment to achieve insulin independence for type 1 diabetic patients.

In the next phase, the research shifted from organ to islet transplantation. As islets comprise 1% to 2% of the pancreas, the transplantation could be achieved through a minimally invasive process. However, there is a significant challenge regarding the survival of islets. Cells need a natural microenvironment to stay functional, but direct transplantation exposes them to immunological attack. Hydrogels, with their tissue-like properties, showed the promise of being a natural barrier. Hence, extensive research was undertaken to encapsulate the islets in hydrogels. Yet this manipulation was not foolproof. Even a fully protected β cell cannot keep the insulin level normal. In a healthy individual, insulin production is regulated by β cells only. Meanwhile, α, somatostatin, and ghrelin cells also significantly influence this process. Bioprinting, which can create mini-organs comprising different kinds of cells, mimicking their natural orientation, was thought to resolve this problem. However, this technique is still in its infancy and is likely to need considerable research investment before it finds a place in regular clinical practice.

The percentage of cell survival improved. The process of transplantation was minimally invasive. Moreover, allogeneic islets could reduce the gap between supply and demand. However, the efficiency of the process is less than desirable.

With the advances in stem cell research, another promising avenue for achieving insulin independence has opened the production of insulin-producing cells from stem cells. In this strategy, insulin-producing cells are biotechnologically expanded to transplantation quality β cells. Stem cells produce the supporting cells, which promote insulin homeostasis. However, this technique requires a high volume of cells per patient because of the exponential post-transplantation loss of these cells. Another major risk of using progenitor cells is neoplasia. Considering these risks, it is highly likely that progenitor cells will remain experimental for some more time until the pros and cons of the technique are properly studied. At present, extensive clinical trials are on to assess the technique's efficacy (Table 2).

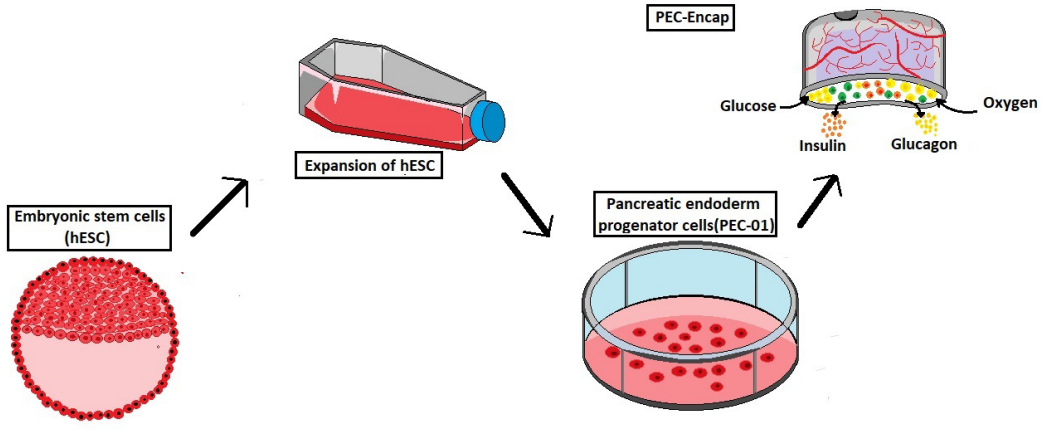

Figure 2. Method of development of PEC-Encap device created by ViaCyte

Table 2. Some important clinical trials on islet transplantation (active/completed)

S.NO	NCT Number	Study title	Phase	Study status	Purpose of study	Biological/ drug interventions	Sponsor	Start date	Locations
1	NCT01571817	Pancreatic islet transplantation into the gastric submucosa	Phase 1	Completed	To evaluate the safety and efficacy of the gastric submucosal space as a novel site for clinical islet transplantation compared with the conventional intraportal transplant site.	Isolated human pancreatic islets	Andrew Posselt	2012-04	University of California, San Francisco, California, United States
2	NCT00708604	Islet after kidney transplantation (iak) in patients with type 1 diabetes	Phase 1	Completed	To determine the safety of islet transplantation in patients with type 1 diabetes who have had a successful kidney transplant and have been maintained for at least three months on anti-rejection medications (combination of sirolimus, tacrolimus, MMF or prednisone).	Islet cell transplantation	City of Hope Medical Center	2005-08	City of Hope Medical Center, Duarte, California, United States
3	NCT01722682	Bone marrow vs liver as site for islet transplantation	Phase 1, Phase 2	Completed	To evaluate the safety and efficacy of bone marrow (BM) as site for pancreatic islet transplantation in humans and to compare BM and liver as sites for islet transplantation in T1D patients.	Human pancreatic islet transplantation	Ospedale San Raffaele	2012-06	Ospedale San Raffaele, Milan, Italy
4	NCT01909245	Islet cell transplant for type 1 diabetes	Phase 2	Active not recruiting	To determine if islet cell transplantation using ATG or alemtuzumab, along with additional medications to prevent the body from rejecting the transplanted cells,	Biological: Allogenic human islet cells | DRUG: Immunosuppressive agents, gastrin 17	City of Hope Medical Center	2013-7	City of Hope Medical Center, Duarte, California,United States
5	NCT05219409	Effects of sitagliptin in relatives of T1D patients	Phase 2 Phase 3	Not yet recruiting	To investigate if Sitagliptin can delay progression to overt T1D in screened relatives of T1D patients classified as high-risk of developing T1D.	Drug: Sitagliptin | device: Professional CGM	University of Milan	2023-07	ASST FBF Sacco, Milan, Italy
6	NCT00133809	Islet transplantation in type 1 diabetics using the Edmonton protocol of steroid free immunosuppression	Phase 2	Completed	To study the ability of islet transplantation to restore glycemic control and achieve insulin independence in type 1 diabetic subjects with life-threatening hypoglycemia and unawareness, or recurrent hyperglycemia with ketoacidosis.	Drug: Transplantation of human islets	Emory University	2002-07	The Emory Transplant Center, Atlanta, Georgia, United States
7	NCT04078308	Mesenchymal stem cells transplantation in newly diagnosed type-1 diabetes patients	Phase 1, Phase 2	Unknown	To examine the safety and efficacy of transplantation of MSCs in new-onset type 1 diabetes patients	Biological: Intravenous injection of autologous mesenchymal stem cells | other: Intravenous injection of placebo	Royan Institute	06-07-2015	Royan Institute, Tehran, Islamic Republic of Iran
8	NCT00789308	Safety and effectiveness of low molecular weight sulfated dextran in islet transplantation	Phase 2	Completed	To assess the safety and effectiveness of low molecular weight sulfated dextran (LMW-SD) on post-transplant islet function in people with type 1 diabetes who have responded to intensive insulin therapy.	DRUG: Low molecular weight sulfated dextran (LMW-SD) ,heparin, (Mycophenolate mofetil)/OR RapamuneÂ® (Sirolimus)/(Tacrolimus)/Cyclosporine, (anti-thymocyte globulin) - at 1st transplant | DRUG: Basiliximab at 2nd or 3rd transplant, (Enoxaparinsodium), (Acetylsalicylicacid- ASA), (Etanercept)	National Institute of Allergy and Infectious Diseases (NIAID)	11-07-2008	University Hospital Rikshospitalet, Oslo, Norway | Karolinska University Hospital, Stockholm, Sweden | Uppsala University Hospital, Uppsala, Sweden

S.NO	9	10	11	12	13	15	16	17
NCT Number	NCT00006505	NCT02803905	NCT01630850	NCT00678990	NCT00321256	NCT04198350	NCT00276250	NCT00434850
Study title	Solitary islet transplantation for type 1 diabetes mellitus using steroid sparing immunosuppression	Islet transplant alone in omentum	Islet transplantation in patients with "brittle" type i diabetes	Heparinized Islets in Clinical Islet Transplantation	Human islet transplantation in brittle type 1 diabetes mellitus. the gragil 2 study.	Pancreatic islet transplantation to the anterior chamber of the eye	Islet transplantation using abatacept	Peritransplant deoxyspergualin in islet transplantation in type 1 diabetes
Phase	Phase 2	Phase 2	NA	NA	Phase 1, Phase 2	NA	Phase 2	Phase 2
Study status	Completed	Active Not Recruiting	Recruiting	Unknown	Completed	Active Not Recruiting	Completed	Completed
Purpose of study	To test whether a new islet transplant procedure will enable patients with type 1 diabetes mellitus to stop insulin therapy.	To test the efficacy of islet transplantation either into the liver through the portal venous circulation directly into the omentum	To learn about the safety of islet transplantation for Type 1 diabetes mellitus,	To investigate safety and efficacy of allogeneic islet transplantation using islets coated with immobilised heparin to protect the islets from being attacked by the immediate defence systems in blood (coagulation and inflammation),	To assess the efficacy of transplanting allogenic pancreas islets tin patients with brittle type 1, insulin-dependent diabetes mellitus and to improve their metabolic control.	To assess the safety of human pancreatic islet transplantation into the anterior Chamber of the Eye of participants with T1D.	Islet transplantation in type 1 diabetics with hypoglycemic unawareness using abatacept as a part of a novel calcineurin-inhibitor-sparing immunosuppressive regimen.	To assess the safety and efficacy of deoxyspergualin (DSG), an immunosuppressant drug, on post-transplant islet function in people with type 1 diabetes who have not responded to intensive insulin therapy.
Biological/ drug interventions	Drug: Islet transplantation	Biological: islet transplantation	Biological: Allogenic islet cells (human, U. Chicago)|procedure: Intraportal infusion of islet cells	Transplantation of islets with heparin coating	Human pancreatic islet transplantation	Islet implantation	Drug: Efalizumab, Abatacept, Belatacept	Biological: Allogeneic pancreatic islet cells,drug: Deoxyspergualin|biological: Antithymocyte globulin|biological: daclizumab or Basiliximab|drug: Sirolimus|drug: Tacrolimus|Biological: Etanercept
Sponsor	National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)	Lorenzo Piemonti	University of Chicago	Corline Biomedical AB	University Hospital, Grenoble	Imperial College London	Emory University	National Institute of Allergy and Infectious Diseases (NIAID)
Start date	16-11-2000	2016-04	2012-05	2019-01	2003-07	01-09-2022	2005-12	2006-10
Locations	National Institutes of Health Clinical Center, 9000 Rockville Pike, Bethesda, Maryland,, United States	IRCCS San Raffaele Scientific Institute, Milan, Italy	University of Chicago Medical Center, Chicago, Illinois, 60637, United States	Sweden	France,Switzerland	Imperial College London, Imperial College Healthcare NHS Trust, London, W2 1PG, United Kingdom	Emory University, Atlanta, Georgia, 30322, United States	University of Californinia, San Francisco, San Francisco, California, United States|Northwestern University, Chicago, Illinois, United States|University of Minnesota, Minneapolis, Minnesota, United States

S.NO	NCT Number	Study title	Study status	Phase	Purpose of study	Biological/ drug interventions	Sponsor	Start date	Locations
18	NCT00175266	Islet transplantation using cam-path-1h and infliximab induction	Completed	Phase 2	To improve the safety and efficacy of clinical islet-alone transplantation by minimizing dependence on calcineurin-inhibitor therapy - thereby avoiding potential nephrotoxicity, and furthermore improving success with single-donor islet infusions by avoiding all diabetogenic immunosuppression.	Drug: Alemtuzumab | Procedure: Islet transplant | DRUG: infliximab	University of Alberta		University of Alberta - Clinical Islet Transplant Program, Edmonton, Alberta, T6G2C8, Canada
19	NCT02000687	Long term surveillance of islet transplant recipients following complete graft loss	Recruiting	NM	This is a single-center, prospective, open label study in islet transplant recipients following islet graft loss.		Rodolfo Alejandro	2008-12	Diabetes Research Institute, Miami, Florida, United States
20	NCT05294822	Autologous regenerative islet transplantation for insulin-dependent diabetes	Recruiting	NA	To evaluate autologous regenerative islet transplantation for insulin-dependent diabetes mellitus.	Procedure: Autologous regenerative islet transplantation for insulin-dependent diabetes mellitus	Shanghai Changzheng Hospital	30-09-2019	Shanghai Changzheng Hospital, Shanghai, Shanghai, China
21	NCT01123187	Islet cell transplantation in patients with type i diabetes with previous kidney transplantation	Completed	NA	To confirm the efficacy and safety of sequential islet allotransplantation with steroid free immunosuppression in patients with previous kidney transplantation.	Procedure: Islet transplantation	University Hospital, Lille	2003-03	University Hospital of Lille, Lille, Nord, France
22	NCT00214786	Pancreatic islet cell transplantation	Completed	Phase 1	To assess a novel approach to immunosuppression in allogenic pancreatic islet cell transplant recipients.	Biological: Islet cell transplantation	Baylor Research Institute	2005-04	Baylor Regional Transplant Institute - Baylor University Medical Center, Dallas, Texas, United States
23	NCT00530686	Pancreatic islet cell transplantation - a novel approach to improve islet quality and engraftment	Completed	Phase 1	To assess a novel approach to immunosuppression in allogenic pancreatic islet cell transplant recipients.	Drug: Islet cell transplantation	Baylor Research Institute	2008-07	Annette C. & Harold C. Simmons Transplant Institute - Baylor University Medical Center, Dallas Texas, USA - Baylor All Saints Medical Center, Fort Worth Texas, USA, Dallas, Texas, 75246, United States
24	NCT01967186	Intraportal or intramuscular site for islets in simultaneous islet and kidney transplantation	Unknown	NA	To compare a new transplantation site (intramuscular in the arm) to the golden standard (the liver) in patients undergoing kidney transplantation from the same donor.	Procedure: Intraportal islet transplantation | procedure: Intramuscular islet transplantation | procedure: Intramuscular transpl with stemcells | PROCEDURE: Kidney transplantation	The Nordic Network For Clinical Islet Transplantation	2007-04	Kidney Transplant Unit, Helsinki University Hospital, Helsinki, Finland

S.NO	NCT Number	Study title	Phase	Study status	Purpose of study	Biological/ drug interventions	Sponsor	Start date	Locations
25	NCT02064309	An open label, pilot investigation, to assess the safety and efficacy of transplantation of macro-encapsulated human islets within the bioartificial pancreas beta-air in patients with type 1 diabetes mellitus	Phase1 , Phase 2	Active not recruiting	To investigate the safety of implantation of the human islet containing device Beta-Air in type 1 diabetic subjects and to check its efficacy in providing improved glycemic control in T1DM patients	Device: Beta-Air device for encapsulation of transplanted human islets	Uppsala University Hospital	2014-02	Uppsala University Hospital, Uppsala, Sweden
26	NCT03513939	A safety, tolerability and efficacy study of sernova's cell pouchâ„¢ for clinical islet transplantation	Phase 1, Phase 2	Recruiting	To demonstrate the safety and tolerability of islet transplantation into the Cell Pouch in subjects with history of severe hypoglycemic episodes. 2. To establish islet release criteria that accurately characterize the islet product and are predictive of clinical transplant outcomes into the Cell Pouch.	Combination_product: Sernova cell pouch	Sernova Corp	07-02-2019	University of Chicago Medical Center, Chicago, Illinois, United States
27	NCT02846571	Pancreatic islet transplantation into the anterior chamber of the eye	Phase 1, Phase 3	Recruiting	To perform intraocular islet transplantation with a single dose of 1000 - 2000 Islet Equivalents (IEQ)/ kg recipient body weight (BW).	Biological: Human pancreatic islet transplantation	Midhat H Abdulreda	05-12-2019	Bascom Palmer Eye Institute, Miami, Florida, United States|Diabetes Research Institute, University of Miami Miller School of Medicine, Miami, Florida, United States
28	NCT00468117	Efficacy of islet after kidney transplantation	Phase 3	Completed	To assess the benefit of islet transplantation in type 1 diabetic (T1D) kidney transplant recipients.	Procedure: Islet transplantation|Biological: Anti-thymocyte globulin|biological: Daclizumab Or basiliximab|biological: etanercept|biological: allogenic human purified pancreatic islets	National Institute of Allergy and Infectious Diseases (NIAID)	2007-01	United states, Canada
29	NCT01817959	Study to assess efficacy & safety of reparixin in pancreatic islet transplantation	Phase 3	Completed	To assess whether Reparixin leads to improved transplant outcome as measured by glycaemic control following intra-hepatic infusion of pancreatic islets in patients with Type 1 diabetes (T1D). The safety of Reparixin in the specific clinical setting was also evaluated.	DRUG: Reparixin|drug: placebo	DompÃ© Farmaceutici S.p.A	2012-10	United States,Czechia, Italy,Sweden, United Kingdom
30	NCT03162237	Safety and efficacy study of islets xenotransplantation	NA	Completed	To evaluate the efficacy and safety of neonatal pig islets being used as a donor cultured with modified culture medium	Other: Porcine islets|other: autologous treg	Wei Wang,MD	2013-07	Cell Transplantation and Gene Therapy Institute, Changsha, Hunan, China

S.NO	NCT Number	Study title	Phase	Study status	Purpose of study	Biological/ drug interventions	Sponsor	Start date	Locations
31	NCT03791567	Islet Transplantation in type i diabetic patients using the university of Illinois at Chicago (UIC) protocol	NM	Approved for marketing	To demonstrate safety and efficacy of allogeneic islet transplantation in improving glycemic control in Type 1 diabetic patients using the UIC protocol.T	Donislecel (allogeneic islets of Langerhans for transplant)	CellTrans Inc.		University of Illinois at Chicago Medical Center, Chicago, Illinois, United States
32	NCT00706420	Islet transplantation alone (ITA) in patients with difficult to control type i diabetes mellitus using a glucocorticoid-free immunosuppressive regimen	Phase 1	Active not recruiting	To evaluate the safety and effectiveness of islet cell transplantation alone (ITA) in patients with difficult to control type I diabetes.	Islet Transplantation+Immunosuppression|biological: Islet cell transplantation	City of Hope Medical Center	07-04-2004	City of Hope Medical Center, Duarte, California, United States
33	NCT00501709	Prevention of autoimmune destruction and rejection of human pancreatic islets following transplantation for insulin dependent diabetes mellitus	Phase 1, Phase 2	Completed	To improve islet transplantation as a treatment for Type 1 Diabetes by using a new combination of immunosuppressive drugs that have been successful in treating other autoimmune diseases and in preventing kidney transplant rejection.	Drug: Belatacept and Raptiva	University of California, San Francisco	2007-02	University of California, San Francisco, California, United States
34	NCT02402439	Treatment of type i diabetes by islet transplantation into the gastric submucosa study protocol	Phase 1	Active not recruiting	To gain initial clinical experience regarding the safety and efficacy of treating type I diabetes in people who have received a kidney transplant by transplanting islets into a new transplant site in the stomach (gastrointestinal submucosa).	Drug: Islet cells|procedure: Islet transplantation into the gastrointestinal submucosa	Andrew Posselt	2016-03	University of California, San Francisco, California, United States
35	NCT00315627	Steroid-free and long-term calcineurin-free trial in islet cell transplantation	Phase 2	Completed	To reverse hyperglycemia and insulin dependency in patients with type 1 diabetes mellitus through islet transplantation utilizing steroid free, calcineurin-inhibitor free immunosuppression and to assess the long-term function of successful islet transplants in patients with type 1 diabetes mellitus utilizing islets that have undergone a period of culture.	Drug: Islet transplantation	Rodolfo Alejandro	2005-07	Diabetes Research Institute, Miami, Florida, United States
36	NCT01345227	Bone marrow as an alternative site for islet transplantation		Completed	To evaluate safety and feasibility of bone marrow (BM) as site for islet transplantation (Tx) in humans.	Procedure: Intra bone marrow islet infusion	Ospedale San Raffaele	2009-08	IRCCS San Raffaele, Milan, Italy
37	NCT04786262	A safety, tolerability, and efficacy study of VX-880 in participants with type 1 Diabetes		Recruiting	To evaluate the safety, tolerability and efficacy of VX-880 infusion in participants with Type 1 diabetes mellitus (T1D) and impaired awareness of hypoglycemia (IAH) and severe hypoglycemia.	Biological: VX-880	Vertex Pharmaceuticals Incorporated	29-03-2021	United States|Canada/Germany/Netherlands/Switzerland

S.NO	38	39	40	41	42	43	44
NCT Number	NCT00160732	NCT00214253	NCT02763423	NCT00646724	NCT03698396	NCT02854696	NCT00446264
Study title	Allogenic islet cell transplantation	Islet transplantation in type 1 diabetic patients	Allogeneic umbilical cord mesenchymal stem cell transplantation for type 1 diabetes with diabetic ketoacidosis	Cotransplantation of islet and mesenchymal stem cell in type 1 diabetic patients	Islet Transplant in Patients With Type I Diabetes	Health Economic Analysis of Islet Cell Transplantation for the Stabilization of the Severe Forms of Type 1 Diabetes	Islet Allotransplantation With Steroid Free Immunosuppression
Phase	Phase 1, Phase 2	Phase 1	NA	Phase 1, Phase 2	Phase 1Phase 3	Phase 3	Phase 2
Study status	Active not recruiting	Completed	Unknown	Unknown	RECRUITING	Active not recruiting	Completed
Purpose of study	To determine the safety of transplanting human islet cells for controlling hyperglycemia in brittle and/or complex patients with type 1 diabetes. The "Edmonton Protocol" of using specific anti-rejection drugs without steroids is also being evaluated.	To check the efficacy of treatment of islet transplant recipients with thiazolidinediones (i.e. pioglitazone) enhance post-transplant islet function and reduce the number of islets necessary to achieve adequate metabolic control? 3) To check whether cadaver donor pancreases, which are ordinarily discarded and not used for pancreas transplantation be used for islet transplantation	To determine whether allogeneic umbilical cord mesenchymal stem cell transplantation is effective in the treatment of patients with severe type 1 diabetes.	To evaluate the safety and efficacy of Cotransplantation of Islet and Mesenchymal Stem Cell in Type 1 Diabetic Patients.	To demonstrate that islet transplantation can be performed safely and reliably achieves better glycemic control than state-of-the-art insulin treatment in the management of type 1 diabetic patients with brittle control	To perform a cost-utility analysis to compare islet cell transplantation versus best medical treatment (defined as Sensor augmented pump therapy) for patients with brittle type1 diabetes.	To confirming the consistent short term efficacy and safety of sequential islet allotransplantation with steroid free immunosuppression in patients with severe T1D.
Biological/ drug interventions	Drug: Allogenic islet cells (human, U. Chicago)|procedure: Intraportal infusion of islet cells	Drug: Thiazolidinedione	Umbilical cord mesenchymal stem cell	Biological: cotransplantation of islet and mesenchymal stem cell	Biological: Allogenic islet cell transplantation	Islet graft|drug: Best medical care	Procedure: islet transplantation|DRUG: daclizumab - sirolimus - tacrolimus
Sponsor	University of Chicago	University of Wisconsin, Madison	The Affiliated Nanjing Drum Tower Hospital of Nanjing University Medical School	Fuzhou General Hospital	Kenneth Brayman, MD	University Hospital, Grenoble	University Hospital, Lille
Start date	2003-10	2002-02	2009-01	2008-01	01-08-2019	07-07-2016	2003-05
Locations	The University of Chicago Hospitals, Chicago, Illinois, United States	University of Wisconsin, Madison, Wisconsin, United States	The affiliated Nanjing Drum Tower Hospital of Nanjing University Medical School, Nanjing, Jiangsu, China	Fuzhou General Hospital, Fuzhou, Fujian, China	University of Virginia, Charlottesville, Virginia,United States	France|Switzerland	University Hospital of Lille, Lille, France

S.NO	NCT Number	Study title	Study status	Phase	Purpose of study	Biological/ drug interventions	Sponsor	Start date	Locations
45	NCT01241864	Islet transplantation in type 1 diabetic kidney allograft	Recruiting	Phase 2	To learn about the safety of islet transplantation when performed after kidney transplantation,	Biological: Allogenic islet cells (human, U. Chicago)|procedure: intraportal infusion of islet cells	University of Chicago	2010-12	The University of Chicago, Chicago, Illinois, United States
46	NCT01047865	Type 1 diabetes recurrence in pancreas transplants	NM	Recruiting	To test the hypothesis that humoral and cellular islet-specific responses are an early risk factor for the recurrence of autoimmunity and hyperglycemia in simultaneous pancreas-kidney (SPK) recipients independent of alloimmunity.		University of Miami	2005-05	University of Miami Miller School of Medicine Transplant Clinic, Miami, Florida, United States
47	NCT03977662	Pancreatic islets and parathyroid gland co-transplantation for treatment of type 1 diabetes	Recruiting	Phase 1, Phase 2	To test the hypothesis that co-transplantation of allogeneic parathyroid gland with adult pancreatic islets (derived from same deceased donor) in the IM site in people with Type 1 diabetes with functioning kidney and/or liver transplants is safe and leads to insulin independence.	Combination_product: Co-transplantation of PTG with pancreatic islets	Peter Stock	01-07-2019	University of California, San Francisco, California, United States
48	NCT05990530	Allogeneic transplantation of expanded pancreatic islet cells	Recruiting	Phase 2	To evaluate the efficacy and safety of allogeneic pancreatic islet cells transplantation in patients with "brittle" type 1 diabetes.	Biological: YD02-2022	Shanghai Jiao Tong University School of Medicine	22-02-2023	Department of Endocrinology and Metabolic Diseases, Ruijin Hospital, Shanghai Jiao-Tong University, Shanghai, China
49	NCT00692562	Simultaneous islet-kidney transplantation in patients of type 1 diabetes with end-stage renal disease	Completed	Phase 1, Phase 2	To evaluate the efficiency and safety of simultaneous islet-kidney transplantation in patients of type 1 diabetes with end-stage renal disease using a glucocorticoid-free immunosuppressive regimen with alemtuzumab induction.	Simultaneous islet-kidney transplantation	Fuzhou General Hospital	2005-06	Fuzhou General Hospital, Fuzhou, Fujian, China
50	NCT01897688	A Phase 3 Single Center Study of Islet Transplantation in Non-uremic Diabetic Patients	Active not recruiting	Phase 3	To determine the safety and effectiveness of islet transplantation, combined with immunosuppressive medications, specifically using Campath as induction, for treating type 1 diabetes in individuals experiencing hypoglycemia unawareness and severe hypoglycemic episodes.	Biological: Islet cell transplant	Northwestern University	2012-06	Northwestern University, Chicago, Illinois, United States
51	NCT00315588	Islet cell transplantation in patients with type i diabetes with previous kidney transplantation	Completed	Phase 2	To reverse hyperglycemia and insulin dependency, by islet cell transplantation, in patients with type 1 diabetes mellitus who have a stable kidney allograft.	DRUG: Islet transplantation	Rodolfo Alejandro	2000-12	Diabetes Research Institute, Miami, Florida, United States
52	NCT00021788	Islet cell transplantation alone in patients with type i diabetes mellitus: steroid-free immunosuppression	Completed	Phase 2	Islet cell transplantation in patients with type 1 diabetes mellitus	Procedure: Islet cell transplantation	National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)	2000-07	University of Miami Diabetes Research Institute, Miami, Florida, United States

S.NO	53	54	55	56	57	58	59	60
NCT Number	NCT00265473	NCT03444064	NCT00464555	NCT00679042	NCT00888628	NCT00566813	NCT00288977	NCT00623610
Study title	MGA031, sirolimus and tacrolimus in islet transplantation	Polytreg immunotherapy in islet transplantation	Strategies to Improve Islet Survival	Islet Transplantation in type 1 diabetic patients using the university of illinois at chicago (uic) protocol	Study of islet transplantation in type 1 diabetic kidney transplant recipients	Islet transplantation in type 1 diabetic patients using the Edmonton protocol of steroid free immunosuppression	Islet transplantation in type 1 diabetic recipients of kidney transplants	Beta-cell transplantation in pre-uremic patients with type 1 diabetes
Phase	Phase 1, Phase 2	Phase 1	Phase 2	Phase 3	Phase 1, Phase 2	Phase 1, Phase 2	NA	Phase 1, Phase 2
Study status	Completed	Active Not Recruiting	Completed	Active Not Recruiting	Completed	Completed	Completed	Completed
Purpose of study	To evaluate the safety and efficacy of immunotherapy with the anti-CD3 monoclonal antibody hOKT3$\hat{\gamma}^{3}$1 (Ala-Ala), (currently called MGA031) combined with sirolimus and tacrolimus in preventing rejection and autoimmune destruction of deceased donor pancreatic islet transplants in type 1 diabetic recipients.	To assess the safety and feasibility of intravenous infusion of ex vivo-selected and ex vivo-expanded autologous PolyTregs in islet transplant patients. The other goal is to assess the effect of Tregs on beta cell function in islet transplant patients.	To determine the safety and effectiveness of islet transplantation, combined with immunosuppressive medications and medications to support islet survival	To demonstrate the safety and efficacy of allogeneic islet transplantation in improving glycemic control in Type 1 diabetic patients using the UIC protocol.	To set up islet transplantation in patients who have had a kidney transplant and who are using an immunosuppressive regimen that works	To reproduce the Edmonton protocol to demonstrate that pancreatic islets isolated at UIC are safe and of sufficient quality to provide reproducible graft function.	To reproduce results of islet transplantation in type one diabetics in patients with a kidney transplant.	To examine whether temporary immunosuppression with ATG, tacrolimus and MMF allows prolonged survival of beta cell allografts in type 1 diabetic patients with early chronic complications of diabetes.
Biological/ drug interventions	Biological: Allogeneic Islets of Langerhans	Biological: PolyTregs	Procedure: Islet transplant|DRUG: Antithymocyte globulin|DRUG: Basiliximab|DRUG: Lisofylline|DRUG: Sirolimus| DRUG: Tacrolimus	Biological: Islets of Langerhans transplantation	Biological: Purified Pancreatic Islets|DRUG: Etanercept	Drug: Islet cell transplant|drug: Islet cell transplant plus	Islet infusion	Islet cell grafts
Sponsor	University of Minnesota	University of Alberta	National Institute of Allergy and Infectious Diseases (NIAID)	CellTrans Inc.	Massachusetts General Hospital	University of Illinois at Chicago	Beth Israel Deaconess Medical Center	Universitair Ziekenhuis and Diabetes Research Center - Brussels Free University-VUB
Start date	2005-11	01-02-2018	2006-12	05-09-2007	2009-05	2004-11	2000-09	2000-09
Locations	University of Minnesota, Minneapolis, Minnesota, United States	University of Alberta, Edmonton, Alberta, T6G 2C8, Canada	University of Miami, Miami, Florida, United States|University of Illinois at Chicago, Chicago, Illinois, United States	University of Illinois at Chicago Medical Center, Chicago, Illinois, United States	Massachusetts General Hospital, Boston, Massachusetts, United States	University of Illinois at Chicago, Chicago, Illinois, United States	Israel	Brussels

S.NO	NCT Number	Study title	Phase	Study status	Purpose of study	Biological/ drug interventions	Sponsor	Start date	Locations
61	NCT00306098	Islet cell transplantation alone in patients with type 1 diabetes mellitus: steroid-free immunosuppression	Phase 2	Active Not Recruiting	1. To assess the long-term safety and function of successful islet cell transplants in patients with Type 1 Diabetes Mellitus; 2. To determine whether the natural history of the microvascular, macrovascular, and neuropathic complications of Diabetes Mellitus are altered following successful transplantation of islet cells 3. To assess the effect of infliximab, etanercept, exenatide in preventing early islet destruction, and thereby eliminating the need for a second donor's islet cells.	Islets	Rodolfo Alejandro	2000-12	University of Miami, Diabetes Research Institute, Miami, Florida, United States
62	NCT00590876	The impact of pancreatic islet cell allotransplantation on cognitive function in type 1 diabetes mellitus	NM	Completed	To determine whether pancreatic islet cell allotransplantation restores normoglycemia (normal blood glucose levels) in Type 1 Diabetic patients	Islets	Yale University	2008-12	Yale University School of Medicine, New Haven, Connecticut, United States|University of Minnesota, Minneapolis, Minnesota, United States
63	NCT04820270	Infusion of autologous t regulatory cells (t reg) at the time of transplantation of allogenic islets of Langerhans	Unknown	Unknown	Open single armed study to investigate safety and feasibility of administrating autologous T regulatory cells at the time of allogenic islet transplantation.	Other: Autologous T regulatory cells	The Nordic Network For Clinical Islet Transplantation	20-08-2018	Karolinska University Hospital, Stockholm, 14186, Sweden|Uppsala University Hospital, Uppsala, Sweden
64	NCT02367534	Islet transplantation through an indwelling catheter in the umbilical vein	Phase 1, Phase 2	Completed	To perform open surgery, catheterize the umbilical vein, and infuse islets into the portal vein.	Umbilical vein catheterization	Fuzhou General Hospital	2008-06	
65	NCT01974674	Allogeneic islet transplantation for the treatment of type 1 diabetes	Phase 2	Unknown	Phase II clinical trial, aiming at evaluating the allogeneic islet transplantation for the treatment of type 1 diabetes.	Allogeneic transplantation of intrahepatic islet	Assistance Publique - HÃ pitaux de Paris	2013-07	Saint Louis hospital, Paris, Ile de France, France
66	NCT00073281	Islet transplantation for patients with type 1 diabetes		Completed	To test whether type 1 diabetes (t1dm) can be reversed in patients with stable renal allografts by islet transplantation.	Islet transplantation	National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)	2003-08	Columbia Presbyterian Medical Center, New York, New York, United States
67	NCT02916680	Pancreatic islet transplantation in the anterior chamber of the human eye - a pilot study	NA	Recruiting	To establish that transplantation of allogeneic pancreatic islet cells into the anterior chamber of a severely visual impaired diabetic human eye is safe and does not cause ophthalmic or systemic complications.	Pancreatic islet transplantation in the anterior chamber	University Hospital Basel, Switzerland	2016-03	University Hospital Basel, Switzerland

S.NO	NCT Number	Study title	Phase	Study status	Purpose of study	Biological/ drug interventions	Sponsor	Start date	Locations
68	NCT00434811	Islet transplantation in type 1 diabetes	Phase 3	Completed	To determine the safety and effectiveness of islet transplantation, combined with immunosuppressive medications, for treating type 1 diabetes in individuals experiencing hypoglycemia unawareness and severe hypoglycemic episodes.	biological: allogeneic pancreatic islet cells, anti-thymocyte globulin, sirolimus,etanercept,basiliximab|drug: tacrolimus |procedurE: Islet transplantation	National Institute of Allergy and Infectious Diseases (NIAID)	2006-10	United states,Canada.
69	NCT00014911	Islet Transplantation for type 1 diabetes	Phase 2	Completed	To Test whether the islet cell transplantation procedures and results from a previous study in Edmonton, Canada, can be repeated.	Procedure: Islet transplantation|drug: sirolimus, tacrolim, daclizumab,sulfamethoxazole, ganciclovir, trimethoprim, pentamidine	National Institute of Allergy and Infectious Diseases (NIAID)	2001-04	United States,Canada,Germany,Italy,Swirzerland

*Studies that were withdrawn and terminated were excluded

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The critical question, "which is a better technique, islet transplantation or stem cell therapy?" is still unanswered. Both methods, bioprinting and stem cell therapy, show the prospect of a lasting cure, and at the current level, both are extremely expensive. A technique that introduces a safer product into the body will likely be more favorable, and cost will be one of the deciding factors.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this review.

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Authors' contributions

All authors contributed equally to preparing this review.

Conflict of interest

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