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Stem Cells Therapy for Diabetes Mellitus Type 1. An Update on Safety and Outcomes

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Abstract

Type 1 diabetes mellitus (T1DM) is the most prevalent chronic autoimmune illness in children and young adults. It is defined by the loss of pancreatic cells, which causes the body to produce insufficient amounts of insulin and lead to hyperglycemia. Patients with T1DM have a great chance of recovery with stem cell therapy. There have been advancements in stem cell-based therapies for T1DM with the development of research on stem cell treatment for a variety of conditions. Before stem cell therapy for diabetic patients is clinically viable, there are still a lot of unresolved problems. In this review, we highlight recent developments in stem cell-based treatments for T1DM as well as methods for creating insulin-producing cells (IPCs) from various precursor cells. The aim of this study is to investigate the safety and outcomes of stem cells therapy for T1DM.

Keywords: Cell therapy; Stem cell; β-cells; HSC therapy; T1DM, Type 1 diabetes mellitus; MSCs therapy; BM-HSC therapy; AHSCT; UC-MSCs; Insulin-producing cells; Pancreatic islets; Transplantation

Abbreviations: **MSCs**- Mesenchymal Stem Cells; **T1DM**-Type 1 Diabetes Mellitus; **IV**-Intravenously; **UC-MSCs-** Umbilical Cord Mesenchymal Stem Cells; **HSCT-** Hematopoietic Stem-Cell Transplantation; **AHST**- Autologous Nonmyeloablative Hematopoietic Stem Cell Transplantation; **WJ-MSCs-** Wharton's Jelly Mesenchymal Stromal Cells; **CB-SCs**- Human Cord Blood-Derived Multipotent Stem Cells; **AHSCT-** Autologous Hematopoietic Stem Cell Transplantation; **IS-AD-MSC**- Insulin-Secreting Mesenchymal Stem Cells; **CBM**-Cultured Bone Marrow;**PEC-01 cells**- pancreatic endoderm cells-01; **HbA1C**- hemoglobin A1c; **FBS**-Fasting Blood Sugar; **PPBS-** Postprandial Blood Sugars **DKA**- Diabetic Ketoacidosis; **SCT**- Stem Cell Transplantation; **IL**-Interleukin; **TNF**- Tumor Necrosis Factor; **GAD-65-** Glutamic Acid Decarboxylase-65; **IA-2-** Islet Antigen-2; , **ZnT8**- The islet-Specific Zinc Transporter Isoform 8; **ICA**- Pancreatic Islet-Cell Antibodies ; **DNA**-Deoxyribonucleic Acid; **GLP-RAs**- Glucagon-Like Peptide-1 Receptor Agonists; **hESCs**-human embryonic stem cells.

Introduction & Background

The earliest known mention of type 1 diabetes dates back to the ancient Egyptians, who described it over 3,000 years ago. It included thirst, increased urine, and weight loss. In ancient India, individuals learned how to utilize ants to test for diabetes by offering them urine. The presence of ants in the urine was a clue that the urine had high levels of sugar. The term for the ailment was "Madhumeha," which means honey urine [1]. The Greek word "diabetes" (to syphon or pass through), which was first recorded by Apollonius of Memphis in the third century before the common (or present) era (B.C.E.), and

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the Latin word "mellitus" (honey or sweet), are the roots of the phrase diabetes mellitus [1]. Thomas Willis expanded the definition of diabetes in 1675 by adding the term "mellitus." This was brought on by the urine's sweet flavor. According to their writings, the ancient Greeks, Chinese, Egyptians, Indians, and Persians had all recognized this delicious taste in urine [2].

Avicenna (980–1037) in Persia presented a thorough explanation of diabetes mellitus in "The Canon of Medicine." In addition to sexual function deterioration and odd appetite, he also mentioned sweet urine [2]. Sir Harold Percival (Harry) Himsworth established type 1 and type 2 diabetes as distinct conditions in his published work in 1936 [2]. Type 1 diabetes, formerly known as insulin-dependent or juvenile diabetes, is less frequent than type 2. Though it typically appears in kids, teens, and young adults, it can occur at any age [3]. The majority of the approximately 422 million individuals with diabetes globally reside in low- and middle-income nations, and diabetes is directly responsible for 1.5 million fatalities annually. Over the past few decades, diabetes has been gradually on the rise in terms of both cases and prevalence [4]. Diabetes affected 422 million people in 2014, up from 108 million in 1980. Diabetes is a significant contributor to renal disease, heart attacks, strokes, blindness, and lower limb amputation. Age-specific diabetes mortality rates increased by 3% between 2000 and 2019. An estimated two million deaths were attributed to diabetes and diabetes-related kidney disease in 2019 [4].

Less research has been done on the risk factors for type 1 diabetes than on type 2 and prediabetes. However, studies suggest that ancestry matters [3]. Type 1 diabetes is thought to result from an autoimmune reaction (the body attacks itself by mistake). The beta cells, which produce insulin in the pancreas, are destroyed by this process. Before any symptoms manifest, this process may continue for months or even years [3]. Due to certain genes, some people are more likely to develop T1DM (traits passed down from parent to kid). Many of them won't get T1DM despite having the gene. T1DM may also be brought on by an environmental trigger, such as a virus [3].

One of the most classic stories of modern medicine concerns T1DM: the discovery of insulin at the University of Toronto in the early 1920s. Charles Best, a medical student, and young surgeon Frederick Banting were reluctantly given lab space and ten beagles to carry out their well-known studies that discovered "isletin" [5]. By far, the most common T1DM treatment approach is manual testing of blood sugar levels followed by sub-cutaneous injections of insulin, repeated throughout the day. Insulin pumps may be used in place of traditional injections, these have the advantage of being able to continuously infuse small amounts of insulin subcutaneously, helping those patients with difficult-to-control glucose levels to better treat their disease [6].

Alongside developments in insulin replacement therapy, there has been a focus on identifying other drugs that can be combined with insulin to reduce hyper/hypoglycemia and improve metabolic variables without increasing adverse events [6]. Of these, promising candidates include metformin and pramlintide, which have a role in glycemic control in T1D and can modestly reduce triglyceride levels, as well as lowering hemoglobin A1c (HbA1c) and supporting weight loss. In addition, glucagon-like peptide-1 receptor agonists (GLP-RAs) combined with insulin can reduce the daily bolus insulin dose required and improve glucose control and weight loss [6]. Thousands of islet transplants — the cell clusters that include the beta cells — have been done since 1966. But patients need lifelong immunosuppression, and many eventually require supplemental insulin. Each year about 1,300 people in the US receive pancreas transplants, but organs are in short supply and powerful immunosuppressant therapy necessary [5]. Gene therapy is a method of treating illnesses by changing one's deoxyribonucleic acid (DNA), which can be done in a few different ways: 1) by replacing a disease-causing gene with a healthy copy of the gene, 2) by inactivating a disease-causing gene that isn't working as it should, or 3) by introducing a new or altered gene into the body to help treat the disease. The first DNA-based insulin gene therapy that might be used to treat T1DM has been validated by the University of Wisconsin School of Medicine and Public Health. [7].

In the future, for efficient therapy of T1DM, there should be adequate control of the production, storage and release of insulin. For this, a careful choice regarding the type of vector using gene therapy is needed. Despite the proven efficiency of viral vectors, they are always associated with adverse effects such as host immunogenicity (Ad) and insertional mutagenesis (RV) [8]. Therefore, optimizations of the viral vectors are still needed to make them safer for T1DM applications. In the case of nonviral vectors, the selection of the components along with the construction of such carriers should be done critically in order to improve the transfection efficiency and to increase the usability of these systems in the future. To further optimize the escape of the genetic material from the cell's endosomes, especially for polyplexes, it will also be essential to determine the precise process of cell endocytosis [8]. Also, a targeted therapy to specifically deliver genetic material will also improve this kind of therapy. Possibly, a more effective treatment could also be obtained by a combination of gene therapy with stem cell therapy. There are promising results around the gene therapy for the treatment of T1DM that should encourage continuous research in this field in order to make this therapy a possibility one in the nearer future [8].

Stem cell transplantation is one of the most promising choices among the many therapeutic modalities used to look for -cell substitutes [9]. Recent studies have shown

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that stem cells may effectively cure T1DM by restoring immunotolerance and maintaining islet -cell activity. Human clinical trials with cGMP-grade stem cell products have demonstrated that stem cell transplantation had positive benefits on T1DM with no overt side effects [9]. In this study, we examine how stem cell transplantation, including the use of mesenchymal stem cells (MSCs), human embryonic stem cells (hESCs), and bone marrow hematopoietic stem cells (BM-HSCs), adipose tissue-derived MSCs, umbilical cord derived mesenchymal stem cells (Uc-MSCs), Warton jelly mesenchymal stem cells (WJ-MSCs, and amniotic stem cells has advanced in recent years to improve immunotolerance and preserve islet -cell function in people with T1DM. The clinical uses of stem cell therapy in the management of T1DM are demonstrated in this review paper.

Review

Methods: A literature search in PubMed Cental (PMC), PubMed, Google search engine, and Google Scholar was carried out using the following keywords: ‘’Pluripotent stem cells’’, ‘’Mesenchymal stem cells’’, ‘’Human embryonic stem’’, ‘’β-cells, Islet cells’’,‘’Stem cell’’, ‘’Diabetes Mellitus type 1’’, DMT1’’. Additionally, the following Medical Subject Headings ("stem cells"[MeSH Terms] OR ("stem"[All Fields] AND "cells"[All Fields]) OR "stem cells"[All Fields]) AND ("therapy"[Subheading] OR "therapy"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields]) AND ("diabetes mellitus, type 1"[MeSH Terms] OR "type 1 diabetes mellitus"[All Fields] OR "diabetes mellitus type 1"[All Fields]). Study selection was in the language (English only), model (humans only), T1DM only, no review articles included. All types of studies were included as long as they were relevant to our study.

Limitations: There were some limitations during the information gathering process for this review. Our data was mostly gathered from papers with open access that were solely published in English, thus it's possible that some pertinent publications with closed access that were written in other languages were overlooked. The Standard Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards for systematic reviews are not applicable to this review article because it is a traditional review.

Result & Discussion

Stem cells are the unspecialized cells that make up the body's matrix and have the capacity to develop into any type of cell in an organism [10]. Induced pluripotent stem cells, adult stem cells, and embryonic stem cells are the three primary categories of stem cells [11]. Due to their pluripotency, embryonic stem cells (ESCs) can develop into any type of cell in the body [11]. Adult stem cells are multipotent, which means they can differentiate into only a few types of bodily cells and not any cells. Scientists create stem cells in the lab known as "induced pluripotent stem cells," or "iPS cells." The term "induced" refers to the process through which normal adult cells, such as skin or blood cells, are taken and reprogrammed in a lab to become stem cells. Just like embryonic stem cells, they can develop into any cell type [11].

An illustration of "adult" stem cells is mesenchymal stem cells (MSCs), which are "multipotent," meaning they can create some types of specialised body cells but not all types [10]. Known also as tissue-specific stem cells, adult stem cells are more specialised than embryonic stem cells. These stem cells often can produce several cell types for the particular tissue or organ in which they reside [12]. Red blood cells, white blood cells, and platelets, for instance, can be produced by hematopoietic stem cells in the bone marrow. However, stem cells in other tissues and organs do not produce red, white, or platelet-producing blood cells, and blood-forming stem cells do not produce liver, lung, or brain cells [12]. In vitro differentiation of ESCs, umbilical cord blood stem cells, iPS, and MSCs into insulin-producing cells was previously demonstrated [13].

MSCs outperform other stem cells in various ways. They are able to affect a variety of immune cell functions, including those of T cells, B cells, dendritic cells, and natural killer cells (NK), demonstrating their strong immunoregulatory capacity both in vitro and in vivo [13]. Recent research has demonstrated that MSCs can prevent diabetes in mice by inducing regulatory T cells. MSCs also have intermediate degrees of MHC class I molecule expression, which enables transplantation of the cells over MHC barriers. Additionally, they had excellent multiplication potential and did not develop tumours following transplantation. Last but not least, MSCs can locate damaged tissues after being delivered intravenously [13]. Because of their proven safety, bone marrow-derived MSCs are the most frequently applied stem cell source today. However, there are several restrictions, including invasive procedures for the donor during harvesting and varying cell quality and proliferative capacity based on the donor's age and health [13]. Bone marrow is not an appropriate stem cell source for autologous cell treatment in the case of children and elderly patients. Due to the fact that a significant quantity of immature cells can be extracted from the umbilical cord without the need for additional surgery, Wharton's jelly-derived MSCs (WJ-MSCs) are emerging as a potential option [13].

Human trials of cell therapy for T1DM began towards the end of 2003, and the Divisions of Immunology and Endocrinology of the Hospital das Clnicas of the Faculty of Medicine of Ribeiro Preto - University of So Paulo - Brazil conducted the world's first study. The study's goal *(Table 1)* was to evaluate the safety and metabolic effects of autologous nonmyeloablative hematopoietic stem cell transplantation (AHST) in patients with newly diagnosed T1DM [14]. As

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a result of receiving AHST, all but one of the 14 patients had enhanced beta cell activity, and the majority of patients experienced sustained insulin independence [14].

After stem cell transplantation in the 15 original and eight additional patients, Couri et al. continued to monitor C-peptide levels to determine if this benefit was caused by maintenance of beta-cell mass [15]. After autologous nonmyeloablative HSCT in patients with newly diagnosed T1DM, C-peptide levels dramatically increased after a mean follow-up of 29.8 months, and the majority of patients had attained insulin independence with good glycemic control [15]. In a case report published in 2009 by Snarski et al., a 28-year-old male patient with a 4-week history of T1DM was reported to be independent from exogenous insulin following treatment with autologous hematopoietic stem cells [16]. Vanikar et al. reported curing T1DM with co-transplantation of cultured bone marrow (CBM) and insulin-secreting mesenchymal stem cells (IS-AD-MSC) produced from adipose tissue in 2010 for the first time using relatively straightforward methods [17]. This prospective open-label clinical trial found that all patients over a mean follow-up of 23 months had a decreased mean exogenous insulin requirement, decreased Hb1Ac, raised serum C-peptide levels, and became free from diabetic ketoacidosis events with mean 2.5 Kg weight gain on typical vegetarian diet and exercise [17].

In a prospective autologous nonmyeloablative hematopoietic stem cell transplantation (AHSCT) phase II clinical trial, 28 T1DM patients between the ages of 14 and 30 were included. They concluded that AHSCT is a successful long-term treatment for insulin dependency *(Table 2)*, but that its effectiveness is higher in individuals who do not already have diabetic ketoacidosis (DKA) at the time of diagnosis [18].

A phase 1/phase 2 open-label clinical trial was carried out by Zhao et al. A single therapy using the Stem Cell Educator's human cord blood-derived multipotent stem cells (CB-SCs) was administered to each of the 15 T1DM patients who were enrolled in the trial. The results of this study demonstrate the safety of Stem Cell Educator therapy, the improvement of metabolic control, and a reduction in autoimmunity that lasts months after a single treatment. Type 1 diabetes can be reversed via islet cell regeneration after immune modulation by cord blood-derived multipotent stem cells [19]. In patients with some remaining pancreatic islet cell activity and patients with no residual pancreatic islet cell function, the results demonstrated a significant improvement of C-peptide levels, decreased median HbA1C values, and decreased median daily doses of insulin [19]. In patients with newly-onset T1DM, Hu et al. evaluated the long-term benefits of the implantation of Wharton's jelly-derived mesenchymal stem cells (WJ-MSCs) from the umbilical cord. According to the findings, WJ-MSC implantation is both safe and effective, and this therapy can help T1DM patients recover the function of their islet cells over a longer period of time. The study's findings demonstrated that the daily insulin dosage gradually decreased during the follow-up period [20].

In addition, Liu et al. presented an analysis of the clinical outcomes of an allogeneic amniotic cell transplant for the management of T1DM in a 26-year-old male in a case report they published in 2013. The patient had been insulin-independent for 6.2 months at the three-month checkup. Furthermore, the insulin dosage was changed to 8 IU/day at the 36-month follow-up [21]. The outcomes of two case reports of the treatment of two children, a 5-year-old girl and a 9-year-old boy, who had had T1DM for four and seven years, respectively, were published in 2014 by Dave et al. The first patient underwent treatment with infusions of hematopoietic stem cells (HSC) from donor bone marrow (BM) who had improved for the first six months before needing more insulin and higher blood sugar levels. The second patient received non-myeloablative preparation with insulin-secreting cells trans-differentiated from autologous adipose tissue-derived MSCs in addition to BM-HSC, and at follow-up of 24.87 months, maintained stable blood sugar levels with a reduced and consistent need for insulin [22].

Furthermore, McCabe et al. presented an interesting case report in 2017. The authors described a case in which a patient with recently-diagnosed T1DM no longer required insulin following allogeneic HSCT for aplastic anemia. Idiopathic aplastic anemia and abrupt development of T1DM were the patient's diagnoses. Allogeneic HSCT was used to treat aplastic anemia, and exogenous insulin injections were the first step in the therapy of T1DM. It's interesting to note that two months after receiving HSCT, the patient's need for exogenous insulin considerably decreased, allowing for the safe discontinuation of insulin medication, and at 24 months after the transplant, the patient was still euglycemic without it [23]. Clinical trials that use insulin-producing stem cells are now very common, although the therapy is always accompanied with an immunosuppressive regimen.

Encapsulating the insulin-producing cells is a reliable method for preventing rejection and the recurrence of autoimmune disease. However, such a technique also exacerbates issues with nutrient supply to the transplanted tissue, with functional impairment brought on by hypoxia, and with cell death in the clumped, extremely metabolically active islet tissue. An "Air" device with a built-in refillable oxygen tank was created to address this issue [24]. In order to assess the safety of implanting the Air device, which contains isolated allogeneic human islets, subcutaneously in patients with well-controlled and simple T1DM, Carlsson et al. conducted a clinical phase 1 research [24]. Four patients received one or two Air devices, each containing the equivalent number of islets, and were then observed for three to six months until the devices were recovered. Device implantation was risk-free and effectively prevented immune

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Table 1: Summary and characteristics of included studies

Authors / year of publication	Type of stem cells used	Type of study	The objectives of the study	Number of patients/age	Mean dose of injected cells	Mode of injection of the stem cells
Voltarelli et al.,2007 [14]	AHST	A prospective phase 1/2 study/ Clinical Trial	To determine the safety and metabolic effects of high-dose immunosuppression followed by AHST in newly diagnosed T1DM.	15 PTs with T1DM (aged 14-31 years)	11 × l06/kg	I/V
Couri et al., 2009 [15]	AHSCT	A prospective phase 1/2 study/ Clinical Trial	To determine C-peptide levels after autologous nonmyeloablative HSCT in patients with newly diagnosed type 1 DM during a longer follow-up	23 PTs with T1DM (aged 13-31 years)	10.52 × l06/kg	I/V
Snarski et al., 2009 [16]	AHSCT	Case report	To investigate the effects of immuno-ablation and transplantation of autologous HSCT on newly diagnosed PT with T1DM	A 28-year-old male with T1DM	An autologous preparation of 3.03×106 CD34+hematopoietic stem cells/kg BM	I/V
Vanikar et al., 2010 [17]	IS-AD-MSC and CBM	A prospective open-labeled clinical trial	The experience of co-transplantation of IS-AD-MSC and CBM for PTs with T1DM	11 (7M/ 4F) PTs with T1DM, in age group: 5 to 45 years of age years	Xenogeneic-free IS-AD-MSC from living donors 1.5 mL, cell counts: 2. 1 × 1 03/μL, with CBM mean quantum: 96.3 mL and cell count: 2 8. 1 × 1 03/μL,	Intraportal infusion of xenogeneic-free IS-AD-MSC from living donors and CBM
Gu et al., 2012 [18]	AHSCT	A prospective phase II clinical trial.	To determine efficacy of AHSCT for T1DM adolescents with DKA at diagnosis.	28 PTs, (14 M / 14 F) with T1DM, aged 14-30 years	5 μg/kg/day until the neutrophil count was >1,000/μL.	IV
Zhao et al. 2012 [19]	Human CB-SCs, Stem Cells Educator	A phase1/phase 2 study, clinical trial	To determine the reversal of T1DM via islet β cell regeneration by cord blood-derived multipotent stem cells	15 PTs with T1DM, age was 29 years (range: 15 to 41)	Blood Cell Separation MCS+, at 35 mL/min to isolate lymphocytes then transferred and exposed to allogeneic CB-SCs and returned to the patient's circulation (2 to 3 mL/ min) with physiological saline.	I/V
Hu et al 2012 [20]	WJ-MSCs	Randomized Controlled Trial	To study the feasibility of WJ-MSCs, safety and preliminary evaluation of the efficacy of the therapy for improving β cell function	29 patients were divided into two groups by randomized blocks, 15 PTs WJ-MSCs treatment group (group I), 14 PTs control group (group II).	The parenteral solution of WJ-MSCs and normal saline in two group were 50 mL, and cell number was between 1.5 and 3.2 × 107 (mean, 2.6 ± 1.2 × 107).	I/V

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Liu et al. 2013 [21]	Allogeneic amniotic cells	Case report	To evaluate the clinical effects of allogeneic amniotic cell transplant for the treatment T1DM	A 26-year-old man with T1DM	Amniotic stem cells suspended in saline (2×10^7 cells in 10 ml)	into the pancreatic dorsal artery
Dave et al. 2014 [22]	1. BM-HSC 2. Autologous adipose tissue-derived MSCs+ BM-HSC	Two case reports	To evaluate the clinical effects of BM-HSC vs autologous adipose tissue-derived MSCs +BM-HSC in patients with T1DM	1. 5-year-old girl with T1DM 2. 9-year-old boy with T1DM	1st total nucleated cells infused were 21×10^6/kg BW and HSC 52.1×10^6/kg BW 2nd nucleated cells were 20.4×106/kg BW, HSC 51.3×106/kg BW and ISC 1.66×104/kg	IV
McCabe et al. 2017 [23]	allogeneic HSCT	Case report	Treatment of idiopathic aplastic anemia with allogeneic HSCT and monitor T1DM.	17-year-old male with new onset of idiopathic aplastic anemia and new onset of T1DM	The dose of allogeneic HSCT n/a	Not mentioned
Carlsson et al. 2018 [24]	βAir device containing allogeneic human pancreatic islets	Clinical trial (phase 1 trial)	To assess the safety and the efficacy of allogeneic transplantation of macroencapsulated human islets within the bioartificial pancreas βAir in T1DM patients	Four patients with T1DM duration >5 years, age >18 years. (2 F/2 M).	βAir devices, each containing 155 000-180 000 islet equivalents (ie, 1800-4600 islet equivalents per kg body weight).	Subcutaneously insertion of βAir device/s
Shapiro et al. 2021 [25]	PEC-01 cells in VC-02 macroencapsulation devices	Clinical trial phase 1/2, open label	To assess the safety, tolerability, and efficacy of VC-02™ in patients with T1DM.	17 PTs aged 22-57 with T1DM >5 years. (9 M/8 F)	Implanted units were either 'sentinel' units or 'dose-finding' units. The dose-finding units with around 75 million PEC-01 cells. Sentinel units loaded with around 6 million PEC-01 cells	Subcutaneously insertion of VC-02 units
Lu et al., 2021 [26]	Allogeneic UC-MSCs	A nonrandomized, open-label, parallel-armed prospective study	To assess the efficacy and safety of one repeated transplantation of allogeneic MSCs in individuals with T1DM	53 PTs (aged 8-55 years) including 33 adult-onset (≥ 18 years) and 20 juvenile-onset T1DM 27 subjects (UC-MSC-treated group) and control group (n = 26) only received standard insulin therapy.	1.0 × 106 cells/kg was given as one single intravenous infusion, repeated again after 3 months	IV
Izadi et al., 2022 [27]	Autologous MSCs	A phase I/II randomized placebo-controlled clinical trial	To assess the safety and efficacy of intravenous injection of autologous bone marrow-derived MSCs in newly diagnosed T1DM patients	21 PTs (age: 8 to 40 years) were enrolled and randomly assigned to receive either MSCs or placebo	two doses of 1 × 106 autologous MSCs per kilogram of the patient's body weight or placebo at weeks 0 and 3	IV

Abbreviations: MSCs- Mesenchymal Stem Cells; **T1DM**-Type 1 Diabetes Mellitus; **IV**-Intravenously; **PTs**-Patients; **PT**-Patient; **UC-MSCs-** Umbilical Cord Mesenchymal Stem Cells; **HSCT-** Hematopoietic Stem-Cell Transplantation; **AHST**- Autologous Nonmyeloablative Hematopoietic Stem Cell Transplantation; **WJ-MSCs-** Wharton's Jelly Mesenchymal Stromal Cells; **CB-SCs**- Human Cord Blood-Derived Multipotent Stem Cells; **AHSCT-** Autologous Hematopoietic Stem Cell Transplantation; **IS-AD-MSC**- Insulin-Secreting Mesenchymal Stem Cells; **CBM**-Cultured Bone Marrow; M- Male; F-Female; PEC-01 cells- pancreatic endoderm cells.

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Table 2: Summary and characteristics of safety and outcome of included studies.

Authors /year of publication	Type of stem cells used	Follow-up period	Outcomes	Side effects
Voltarelli et al.1,2007 [14]	BM-HSC	7- to 36-month follow-up (mean 18.8)	From total 15 PTs: 14 PTs became insulin-free (one to 35 months). 1 PT resumed insulin use one year after AHST. Six months after AHST, the mean total area under the C-peptide response curve was greater than the pretreatment values, and at 12 and 24 months it did not change. Serum levels of HbA1c were maintained at less than 7% in 13 of 14 PTs.	Culture-negative bilateral pneumonia in one PT and late endocrine dysfunction (hypothyroidism or hypogonadism) in two others.
Couri et al., 2009 [15]	AHSCT	7- to 58-month follow-up (mean29.8 months)	From total 23 PTs: 20 PTs became insulin free. 12 PTs maintained this status for a mean 31 months. 8 PTs relapsed and resumed insulin use at low dose. In the continuous insulin-independent group, HbA1c levels were less than 7.0% and C-peptide levels increased significantly. In the transient insulin-independent group, C-peptide levels also increased, which was sustained at 48 months. In this group, 2 PTs regained insulin independence after treatment with sitagliptin, which was associated with an increase in C-peptide levels.	Two PTs developed bilateral nosocomial pneumonia, 3 PTs developed late endocrine dysfunction, and 9 PTs developed oligospermia.
Snarski et al., 2009 [16]	AHSCT	5 months	The PT has remained normoglycemic with no need of exogenous insulin or other hypoglycemic agents since the 3rd week after the procedure, and 5 months during follow-up.	No adverse effects
Vanikar et al., 2010 [17]	IS-AD-MSC and CBM	mean follow-up of 23 months	PTs had a decreased mean exogenous insulin requirement, Hb1Ac, raised serum C-peptide levels and became free of diabetic ketoacidosis events with mean 2.5 Kg weight gain on normal vegetarian diet and physical activities.	No adverse effects
Gu et al., 2012 [18]	AHSCT	Follow-up 4 to 42 months (mean 19.3)	Insulin independence was observed in 15 of 28 patients (53.6%) over a mean period of 19.3 months. The non-DKA Pts achieved a greater complete remission rate than the DKA patients (70.6% in non-DKA vs. 27.3% in DKA, P = 0.051).	Most PTs experienced febrile neutropenia, nausea, vomiting, alopecia, and bone marrow suppression before the transplantation of SCs, as a result of the drugs used for the mobilization and conditioning.
Zhao et al. 2012 [19]	Human CB-SCs, Stem Cells Educator	Follow-up visits were scheduled 4, 12, 24, and 40 weeks after treatment	Raising of C-peptide levels, reduced the median HbA1C values, decreased the median daily dose of insulin. Increased expression of co-stimulating molecules (specifically, CD28 and ICOS), increases in the number of CD4+, CD25+, Foxp3+, Tregs, and restoration of Th1/Th2/Th3 cytokine balance.	No adverse effects
Hu et al. 2012 [20]	WJ-MSCs	At monthly intervals for the first 3 months, then every 3 months for the next 21 months	During follow-up of 21 months, a decrease in insulin requirement in group 1 was achieved, a decrease in Hb1C and glucose level, and an increase in C-peptide level.	No adverse effects

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Liu et al. 2013 [21]	allogeneic amniotic cells	Follow-up at 3, 6,12,24, 36 months	At three months post-transplantation, till 6.2 months patient was insulin free. During a 36-month follow-up, insulin treatment was readjusted to a dosage of 8 IU/day.	No adverse effects
Dave et al.2014 [22]	1. BM-HSC 2. Autologous adipose tissue-derived MSCs+ BM-HSC	Case 1. Follow-up at six, 18 months Case 2. Follow-up over 24.87 months.	Case 1: The patient's FBS/PPBS decreased during the first six months, however, after six months FBS/PPBS started rising along with HbA1c and increased insulin requirement of 32 IU/day at 18 months, however free of DKA episodes. Case 2. Over follow-up of 24.87 months, his FBS/PPBS were stable and insulin requirement of 15 IU/day. He was free of DKA episodes after SCT.	No adverse effects
McCabe et al. 2017 [23]	Allogeneic HSCT	Follow-up at two, months and one-year, two years post-transplant	The exogenous insulin needs were significantly decreased, then safely discontinued. One-year post-transplant, all four pancreatic antibody levels (GAD-65, IA-2, ZnT8, ICA) decreased and three of the four completely normalized. At 24 months (about 2 years) post-transplant, the patient remained euglycemic without insulin therapy.	n/a
Carlsson et al. 2018 [24]	βAir device containing allogeneic human pancreatic islets	Follow-up 3-6 months	Only minute levels of circulating C-peptide were observed and no effects on metabolic control. Fibrotic tissue with immune cells was formed around the capsule. Recovered devices displayed a blunted glucose-stimulated insulin response, and amyloid formation in the endocrine tissue. The βAir device was safe and supported survival of allogeneic islets for months, however, the function of the transplanted cells was limited.	A mild inflammation surrounding the surgical wound.
Shapiro et al. 2021 [25]	PEC-01 cells in VC-02 macroencapsulation devices	Follow-up 3–12 months	Engraftment and insulin expression were observed in 63% of subjects at 3–12 months post-implant. Six of 17 subjects (35.3%) demonstrated positive C-peptide after 6 months post-implant.	Adverse events related to surgical implant or explant procedures (27.9%) or due to immunosuppression (33.7%)
Lu et al., 2021 [26]	Allogeneic UC-MSCs	Follow-up at 3,6.12 months then yearly	At the end of 1-year follow-up, 11/27 (40%) recipients in UC-MSC-treated group maintained clinical remission versus control group (3/26, 11.5%, p = 0.041). HbA1c levels were significantly decreased at 3 months (6.6 ± 0.8%) in the UC-MSC-treated group, but gradually increased to 6.9 ± 1.1% and 7.3 ± 1.3% respectively at 6 and 12 months.	Three adult recipients had mild fever
Izadi et al., 2022 [27]	Autologous MSC	Follow-up at weeks 1, 2, and 4, and months 2, 3, 6, 9, and 12	Significantly reduced the percent of HbA1c. Significantly increased the anti-inflammatory cytokines IL-4 and IL-10 and decreased TNF-α levels.	A mild injection site reaction observed in two patients (one in each group). A grade 3 urticaria was observed in 1PT during the first injection. A mild increase in lymphocytes occurred in 2 PTs and mild hyperkalemia in 4 Pts.

Abbreviations: MSCs- Mesenchymal Stem Cells; **T1DM**-Type 1 Diabetes Mellitus; **IV**-Intravenously; **PTs**-Patients; **PT**-Patient; **UC-MSCs**-Umbilical Cord Mesenchymal Stem Cells; **HSCT**- Hematopoietic Stem-Cell Transplantation; **AHST**- Autologous Nonmyeloablative Hematopoietic Stem Cell Transplantation; **WJ-MSCs**- Wharton's Jelly Mesenchymal Stromal Cells; **CB-SCs**- Human Cord Blood-Derived Multipotent Stem Cells; **AHSCT**- Autologous Hematopoietic Stem Cell Transplantation; **IS-AD-MSC**- Insulin-Secreting Mesenchymal Stem Cells; **CBM**-Cultured Bone Marrow; **M**- Male; **F**-Female; **PEC-01 cells**- pancreatic endoderm cells-01; **HbA1C**- hemoglobin A1c; **FBS**-Fasting Blood Sugar; **PPBS**-Postprandial Blood Sugars **DKA**- Diabetic Ketoacidosis; **SCT**- Stem Cell Transplantation; **IL**-Interleukin; **TNF**- Tumor Necrosis Factor; **GAD-65**-Glutamic Acid Decarboxylase-65; **IA-2**- Islet Antigen-2; , **ZnT8**- The islet-Specific Zinc Transporter Isoform 8; **ICA**- Pancreatic Islet-Cell Antibodies.

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responses and tissue rejection. Beta cells did survive in the device, but there was little impact on metabolic regulation and the levels of circulating C-peptide were very low [24].

Furthermore, Shapiro et al. performed the first-ever phase 1/2 open-label study in humans and demonstrated proof-of-concept that pluripotent stem cell-derived pancreatic endoderm cells (PEC-01) engrafted in T1DM patients develop into islet cells that release insulin in a physiologically controlled manner [25]. Pancreatic endoderm cells generated from pluripotent stem cells were injected subcutaneously in VC-02 macroencapsulation devices, allowing for direct vascularization of the cells. As a result, individuals received therapeutic immunosuppression to prevent allo/auto-immune rejection. At 3–12 months after the implant, engraftment and insulin expression were seen in 63% of patients. As early as six months after the implant, six out of 17 participants showed positive C-peptide levels [25]. The findings of a parallel-armed, nonrandomized, open-label prospective study was published in 2021 by Lu et al. There were 53 participants with T1DM, of which 26 patients were in the control group. While the control group only got normal care based on intense insulin therapy, 27 participants received a first systemic infusion of allogeneic umbilical cord - mesenchymal cells (UC-MSCs), followed by a repeat dose at three months. Three participants in the UC-MSC-treated group reached insulin independence for three to twelve months, according to the results at the one-year follow-up [26]. Additionally, 40.7% of the subjects in the UC-MSC-treated group saw a significant improvement. Additionally, a phase I/II randomised placebo-controlled clinical trial's findings were just published by Izadi et al. In this study, the effectiveness and safety of injecting autologous MSCs from bone marrow into newly diagnosed T1DM patients was evaluated. The outcomes demonstrated reduced HbA1c, a change from pro-inflammatory to anti-inflammatory serum cytokine patterns, an increase in regulatory T-cells in peripheral blood, and improved quality of life [27].

Conclusion

The impressive data gathered from previous and continuing clinical studies provides optimism regarding the future of the exploration into stem cell therapy for T1DM. Over the past few decades, significant progress has been made in our understanding of how β cells develop normally and how to differentiate stem cells to produce β -like cells. However, this field still faces significant difficulties. It is necessary to address the immune system issue, whether by systemic immunomodulation or the use of immunoprotective technologies. Clinical trials should also be conducted to address concerns about the effectiveness and safety of stem cell transplantation, the ideal size of macroencapsulated devices, the ideal dose of stem cells, the type of stem cells, and the duration of the treatment. Additionally, increasing cell survival after transplant is crucial to improving the potential of such technologies.

Stem cell therapy has the potential to be a cutting-edge and effective therapeutic option for the treatment of diabetes in patients with T1DM. Regarding the working mechanism, the length of the therapeutic effect, and the population that will most likely benefit, there is still a great deal of uncertainty. To support these findings, further high-quality and sizable randomized controlled trials should be conducted due to the paucity of available studies. To turn this goal into reality, additional work is required in a range of areas.

Conflict of Interest statement:

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