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Conventional and Alternative Mesenchymal Stem Cell Therapies for the Treatment of Diabetes

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Abstract

Diabetes is a public health problem affecting millions of people around the world. Despite the availability of many antidiabetic medications, the adequate level of control of the disease and management of diabetic patients remain a huge challenge. Because of the limitations of current therapies and the tremendous potential of non-conventional treatments such as stem cell therapy, herein, we review the applications of mesenchymal stem cells (MSCs) in treating diabetes. Owing to their unique regenerative and immunomodulatory properties, MSCs have been widely utilized in numerous applications both in animal models and human clinical trials for the treatment of diabetes. This review will summarize the latest experimental and clinical studies that have provided evidence of the beneficial role of MSCs in diabetes treatment.

Keywords

Clinical trials · Diabetes · Mesenchymal stem cell · Pharmacological · Treatment

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Abbreviations

AHEAD	Action for Health in Diabetes
DPP	Diabetes Prevention Program
EMA	European Medicines Agency
GLP-1	Glucagon-Like Peptide 1
GvHD	Graft Versus Host Disease
HbA1c	Hemoglobin A1c
IDF	International Diabetes Federation
IPCs	Insulin-producing cells
MMTT	Mixed-meal tolerance test
MSC	Mesenchymal stem cell
NIH	National Institutes of Health
NOD	Non-obese diabetic
PPARs	Peroxisome proliferator-activated receptors
SGLT2	Sodium glucose co transporter 2
STZ	Streptozotocin
T1D	Type 1 diabetes
T2D	Type 2 diabetes
TZD	Thiazolidinediones
WHO	World Health Organization

1 Introduction

1.1 Diabetes: A Global Epidemic

Diabetes is a serious public health problem that has been recognized by many health organizations including the WHO as a global epidemic (Bassett 2005). It is a chronic, degenerative pancreatic

disease characterized by elevated blood sugar levels and glucose intolerance (Ribeiro et al. 2010). This metabolic disorder results from defects in insulin secretion, or insulin action, or a combination of both (Olokoba et al. 2012). Millions of people around the world are affected by diabetes and are either unaware of the condition or not receiving the appropriate treatment (Boles et al. 2017). The severity of diabetes is determined based on the degree of hyperglycaemia. Chronic hyperglycaemia associated with uncontrolled diabetes may, over time, lead to serious health damage such as heart diseases and long term damage to the eyes (Retinopathy), kidneys (Nephropathy) and nerves (Neuropathy) (Reddy 2017). Feet ulcers, infections, and gangrene are also experienced in diabetic patients (Reddy 2017). In addition, hypertension, hyperlipidemia, negative nitrogen balance and sometimes ketonuria are often associated with diabetes (Reddy 2017). Prevention of this endocrine disorder and its complications is a major challenge to attain health for all (Wareham and Herman 2016).

Multiple forms of diabetes have been recognized including type 1 and type 2 diabetes (Deepthi et al. 2017). Type 1 diabetes (T1D) is generally an autoimmune disorder caused by absolute insulin deficiency where, the pancreas is not able to produce enough insulin or does not produce insulin at all (Deepthi et al. 2017). The virtual absence of insulin requires patients' dependence on insulin injections to regulate glucose levels in the blood and sustain life and that is why it is also known as insulin-dependent diabetes (Deepthi et al. 2017). It can occur at any age but it is most prevalent among children and young adults under 30 years old (previously known as juvenile or childhood-onset) who have genetic predisposition to develop pancreatic β cell failure (Boles et al. 2017). On the other hand, type 2 diabetes (T2D), is more prevalent than other types of diabetes and accounts for 90–95% of diabetes cases (Fox et al. 2015). It is primarily the result of progressive impairment of glucose regulation because the insulin secreted by the pancreas is not utilized properly by the body (Deepthi et al. 2017). Insulin resistance and insulin deficiency are caused by higher-than-normal blood sugar levels (Calonge et al. 2008; Deepthi et al. 2017). T2D can occur at any age if there are risk factors like obesity, family history and physical inactivity; however, it is most commonly diagnosed in people over 40 years old (known as adult onset diabetes) (Boles et al. 2017). The symptoms are often less recognized or absent until complications arise when the disease has been undiagnosed for many years (Deepthi et al. 2017).

1.2 Diabetes Status

Diabetes is a critical health issue whose prevalence is steadily increasing around the globe (Wild et al. 2004). In 2000, there were 151 million adults living with diabetes worldwide. By 2011, the number of adults with diabetes increased by 142% to around 366 million (Fig. 1). According to the International Diabetes Federation (IDF), people between 20–79 years reported to have diabetes have reached a staggering 463 million representing 9.3% of the global adult population, with half of them are unaware that they suffer from the condition and therefore are at a higher risk of developing serious associated complications leading to 4.2 million deaths in 2019 (IDF Diabetes Atlas 9th edition 2019). Thus, in the past 20 years, diabetic cases have more than tripled among adults. As the population is aging and the rates of obesity are increasing, it is projected that by 2030 the number of adults living with diabetes will increase to 578 million (10.2%) and jump to a staggering 700 million (10.9%) by 2045 if no urgent actions are taken (Saeedi et al. 2019).

It is worth mentioning that high-income countries have the highest prevalence of adult diabetes (10.4%), followed by 9.5% in middle-income countries and 4% in low-income countries as classified by the World Bank Income group (Saeedi et al. 2019). Moreover, diabetes prevalence has been reported to be higher in urban areas (10.8%) than in rural areas (7.2%); although, this gap is narrowing due to urbanization of rural areas (IDF Diabetes Atlas 9th edition 2019). All the data indicates that the incidence of the disease will continue to increase due to rapid economic development, urbanization and a very

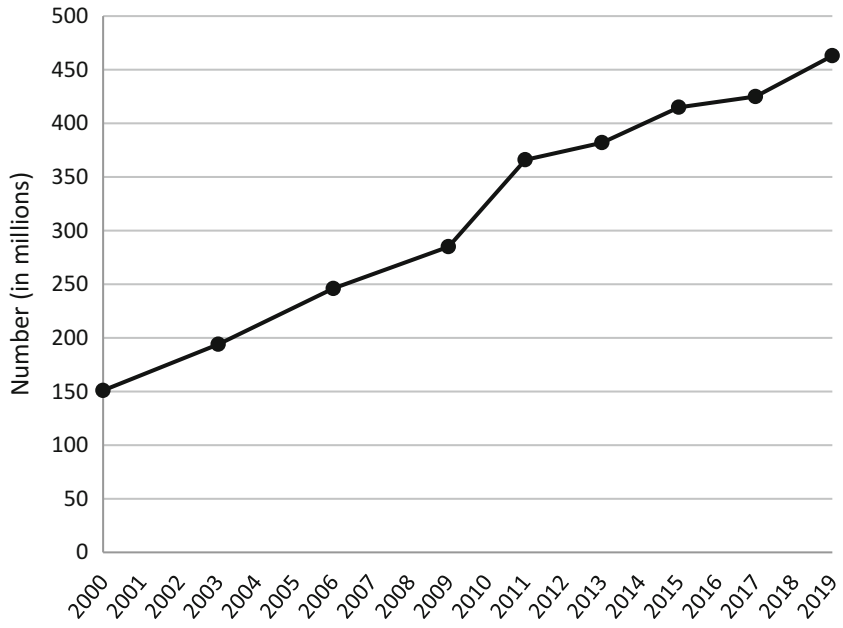

Fig. 1 Total number of adults (in millions) living with diabetes per year from 2000 to 2019

sedentary lifestyle and as long as preventive and control programmes are not effectively followed (King et al. 1998; Nanditha et al. 2016). Thus, all this requires a multisectoral approach to tackle the escalating epidemic (Meng et al. 2019).

2 Non-pharmacological Interventions

Despite the numerous efforts made to control and limit the outspread of diabetes, its high morbidity and mortality rates pose a serious threat which needs to be addressed cautiously (Peng et al. 2018). Diabetes cannot be cured, yet it can be managed with lifestyle modifications at the forefront of the fight against this epidemic especially in T2D.

In the Diabetes Prevention Program (DPP) Randomized Trial that was launched by the National Institutes of Health (NIH) in 1996, the effect of a lifestyle-intervention program through dietary modification and increased physical activity of moderate intensity was investigated in individuals at high risk of developing T2D (DPP Research Group 2002). Results after 2.6 years follow-up showed that the lifestyle modifications were highly effective in delaying or preventing T2D with 58% reduction in its incidence as compared to the placebo group. Astonishingly, these lifestyle changes were significantly more effective than treatment with the anti-hyperglycemic agent, metformin (Knowler et al. 2002). Findings also revealed that after 10 years of follow-up since DPP randomization, diabetes incidence remained lower in the lifestyle group (34%) and in the metformin group (18%) as compared with placebo (DPP Research Group 2009). Another NIH-funded Look AHEAD (Action for Health in Diabetes) trial conducted in T2D patients showed improved hemoglobin A1c (HbA_1c) levels and reduced need for anti-diabetic drugs in the intensive lifestyle intervention group compared with Diabetes Support and Education group (Espeland et al. 2007; Wing et al. 2013).

Yet, sometimes lifestyle modifications are not enough and pharmaceutical interventions are recommended to control hyperglycaemia and prevent disease progression and complications (Solis et al. 2019). The type of diabetes along with its degree of severity affects the type of treatment prescribed (Solis et al. 2019).

3 Pharmacological Diabetes Treatment Options

Several types of oral hypoglycaemic agents have been used in the treatment of T2D. The first line of treatment in patients with T2D is the biguanide, metformin, which was FDA approved in 1994 (Lipska 2017). It improves insulin sensitivity, enhances the ability of peripheral cells to take in glucose, reduces the production of glucose by the liver and aids in weight loss by suppressing appetite (Giannarelli et al. 2003). Some patients may suffer from abdominal bloating, nausea, vomiting and diarrhoea (Siavash et al. 2017). Moreover; patients with kidney problems or heart diseases are advised to be cautious because metformin is thought to increase the risk of developing lactic acidosis (Lipska 2017). However, a review of trials conducted by Salpeter and colleagues showed no evidence of fatal or nonfatal lactic acidosis in subjects on metformin compared to placebo or non-metformin treatment (Salpeter et al. 2010).

The second line of treatment in patients with T2D is sulfonylureas which can be taken as first-line monotherapy if the patient in not overweight or if metformin is intolerable. It can also be given with metformin if glycaemic control is inadequate (Sola et al. 2015). These hypoglycaemic agents are insulin secretagogues that work by stimulating the pancreatic cells to secrete insulin (Sola et al. 2015). They also enhance insulin effectiveness in the body. Sulfonylureas cannot be prescribed to T1D patients who are not able to produce insulin or patients who have had pancreatectomy (Sola et al. 2015). Glinides are another class of oral hypoglycaemic drugs that have similar mechanism of action to sulfonylureas. Both sulfonylureas and glinides have hypoglycaemia as the most common adverse effect (Tran et al. 2015; Keegan 2018).

Thiazolidinediones (TZD) are oral antidiabetic agents that work by increasing insulin sensitivity through its action on peroxisome proliferator-activated receptors (PPARs) (Bailey 2007). Currently, two TZD drugs (Rosiglitazone and pioglitazone) are available in the United States; however, in 2010, rosiglitazone was suspended by the European Medicines Agency (EMA) as the overall risks outweighed its benefits and FDA decided to restrict its use due to increased risk of cardiovascular events (Bourg and Phillips 2012; Pouwels and Van Grootheest 2012). Additionally, in 2011, pioglitazone was suspended by French and Germany Medicines Agencies due to potential increased risk of bladder cancer (Tang et al. 2018).

Alpha-glucosidase inhibitors (acarbose, miglitol and voglibose) are another class of antidiabetic drugs that inhibit the enzymes responsible for breaking down carbohydrates; thus, decreasing their absorption and digestion and subsequently reducing hyperglycaemia (Laar 2008).

Sodium glucose co transporter 2 (SGLT2) inhibitors are also promising oral anti-hyperglycaemic agents that have been developed for the treatment of T2D. They work by reducing blood glucose through inhibition of the glucose reabsorption at the proximal tubule of the kidneys (Simes and Mac Gregor 2019). Examples include canagliflozin and dapagliflozin which have been FDA-approved since 2013. Glycosuria and natriuresis initiated by the inhibition of glucose reabsorption result in modest improvement in weight and blood pressure (Gallo et al. 2015).

Glucagon-Like Peptide 1 (GLP-1) Receptor Agonists, referred to as incretin mimetics, represent another class of pharmacologic treatment for adults with T2D (Hinnen 2017). Incretin hormones, like GLP-1, stimulate insulin secretion and decrease that of glucagon after an oral glucose load. In T2D, this process is reduced and thus insulin release is decreased (Collins and Costello 2020). Therefore, GLP-1 receptor agonists (e.g. exenatide, liraglutide, lixisenatide, dulaglutide) can be prescribed to increase the action of GLP-1 and thereby enhance insulin response (Hinnen 2017). *In vivo*, GLP-1 is inactivated by the hormone dipeptidyl peptidase-4 (DPP-4). So, DPP-4 inhibitors can also be given to increase insulin secretion by inhibiting the enzymatic degradation of the incretin hormone, GLP-1, thereby increasing postprandial GLP-1 activity (Collins and Costello 2020).

In addition to lifestyle modifications and oral hypoglycaemic agents and because of the progressive nature of diabetes, most of the patients with T2D might require insulin replacement therapy to maintain satisfactory blood glucose levels and attain treatment goals (Blonde et al. 2009). However, hypoglycaemia is again a major common side effect of insulin treatment (McCall 2012).

4 Alternative Diabetes Therapies

Although exogenous hypoglycaemic agents and therapeutic insulin provide control over blood glucose and may prevent complications; none of these strategies are able to mimic the natural activity of endogenous insulin especially in T1D patients who are fully insulin-dependent. Moreover, despite the advances made in pharmacology, these antidiabetic drugs are not without significant adverse effects as shown above (Fonseca and Haggar 2014; Peng et al. 2018). Therefore, there is an urgent need for non-conventional therapies that are safe and effective in combatting diabetes. In particular, stem cell-based therapy holds an immense promise as an alternative possible approach to treat diabetes and alleviate its complications.

Mesenchymal stem cells (MSCs) are at the forefront being the most attractive type of adult stem cells under investigation to tackle diabetes. MSCs have been highlighted because of their self-renewal capacity, multipotentiality, low antigenicity, homing ability, reduced toxicity, and ease of culture and expansion *in vitro* (Chen et al. 2007). Moreover, they are abundant and can be easily isolated from different tissues including bone marrow (BM), adipose tissue (AD), umbilical cord (UC), placenta and dental pulp (Orbay et al. 2012).

4.1 Preclinical Applications of Mesenchymal Stem Cells in Diabetes

The ability of MSCs to differentiate into islet-like cells or functional insulin-producing cells (IPCs), to home and induce regeneration of endogenous pancreatic islet beta cells as well as to protect these cells through immunomodulatory properties, have made MSCs a potential novel cell-based treatment for diabetes (Zanini et al. 2011).

Many groups around the world have investigated MSCs transplantation in animal models of diabetes. Madec and his colleagues assessed the effects of a single dose of MSCs infusion in non-obese diabetic (NOD) mice, an animal model for T1D (Madec et al. 2009). MSCs were able to inhibit autoimmune beta cell destruction mediated by progressive islet infiltration of autoreactive (destructive) T cells and macrophages and subsequently prevent diabetes in the NOD mouse model by induction of regulatory (protective) T cells (Madec et al. 2009). These results were in line with other studies reporting that intravenous administration of MSCs into streptozotocin (STZ)-induced T1D mice reverted hyperglycaemia through suppression in autoreactive T cell levels together with increase in pancreatic regulatory T cells (Ezquer et al. 2012). Other preclinical studies have shown that apart from their immunomodulatory properties, undifferentiated MSCs transplantation alleviated hyperglycaemia in NOD mice via differentiation into pancreatic IPCs (Tsai et al. 2015). A more recent study has demonstrated that direct transplantation of MSCs into the impaired pancreas of STZ-treated rats, improved their differentiation into IPCs (Li et al. 2016). Furthermore, intra-pancreatic MSC transplantation stimulated endogenous pancreatic β-cell regeneration resulting in islet neogenesis (Li et al. 2016).

Authors suggested that MSCs might activate endogenous precursor stem cells by providing a supportive pancreatic microenvironment through direct cell-cell contact or the stem cell secretome (Ezquer et al. 2014; Li et al. 2016).

Despite the large number of preclinical studies showing the beneficial effects of MSCs in animal models of diabetes, there are fewer clinical trials utilizing MSCs for treatment of diabetic patients.

4.2 Clinical Applications of Mesenchymal Stem Cells in Diabetes

Twenty five years ago, in 1995, Hillard Lazarus and his colleagues reported the first phase I clinical trial using bone marrow-derived MSCs in human subjects with hematologic malignancies (Lazarus et al. 1995). Since then, clinical trials using MSCs have been rising exponentially to treat a large number of diseases including hematologic, neurodegenerative, autoimmune, liver, lung and kidney diseases. In fact, it was not until 2011 that MSCs (Hearticellgram®-AMI) were approved by Korean Food and Drug Administration for the treatment of acute myocardial infarction. This was followed by Canada and New Zealand granting marrow-derived MSCs (Prochymal®, Mesoblast International Sarl.) conditional approval, in 2012, for the treatment of acute Graft Versus Host Disease (GvHD) in paediatric patients (Waltz 2013). Subsequently, in the last decade, a series of clinical trials using MSCs have been running to assess MSCs safety and efficacy in numerous diseases. Since 2010, more than 1000 MSC-based clinical trials have been listed in the clinical trial registry of the U.S. National Institutes of Health (http://www.clinicaltrial.gov/). According to the data reported by the US NIH, 61 MSC clinical trials have been revealed for diabetes in the last 10 years representing 6% of all trials (Fig. 2). These human trials are roughly evenly divided between T1D and T2D where most of them (51 trials) are still in the early phases (phase I, I/II, or II). There are only few phase III trials either have been completed or ongoing. Most of the MSCs employed in these studies are derived from the umbilical cord (33%), followed by the bone marrow (28%) and adipose tissue (25%) (Fig. 2). Other MSC sources such as wharton's jelly, dental pulp or menstrual blood have also been used. A major issue of note is that more than 90% of these trials are small-sized with less than 100 participants per trial.

Herein, we will review a number of clinical studies, registered at clinicaltrials.gov, that were conducted to evaluate the efficacy and safety of MSCs for treatment of both types of diabetes. In T1D, the important clinical goal is to retain the endogenous secretion of insulin; thereby, attaining long term restoration of glucose metabolism and reducing risk of complications such as hypoglycaemic episodes (Carlsson et al. 2015). Carlson and his colleagues reported the first study on the use of systemic MSC treatment for adult patients newly diagnosed with T1D. The randomized controlled trial under the registration number NCT01068951 aimed to assess the safety and therapeutic effect of autologous BM-MSC treatment in new-onset T1D for a period of one year (Carlsson et al. 2015). All patients tolerated the MSC treatment with no observed adverse effects. Besides, MSC-treated patients preserved pancreatic beta cell function as indicated by preserved or even increased C-peptide response to mixed-meal tolerance test (MMTT) at 1-year follow-up. Despite the promising findings, longer follow-up duration is necessary to validate the results (Carlsson et al. 2015). In 2016, Cai et al. conducted a pilot randomized controlled open-label clinical study (NCT01374854) examining the safety and efficiency of allogeneic Wharton's jelly UC-MSCs plus autologous bone marrow mononuclear cell (aBM-MNC) in patients with established T1D rather than new-onset T1D (Cai et al. 2016). At 12-month follow-up, insulin secretion and C-peptide improved in the treated group compared to the standard care control group. Moreover, HbA_1c, fasting blood glucose and exogenous insulin requirement in the experimental group were lower compared with the control group (Cai et al. 2016). Another interesting phase II pilot study (NCT03920397) evaluated the safety and efficacy of allogenic AD-MSCs

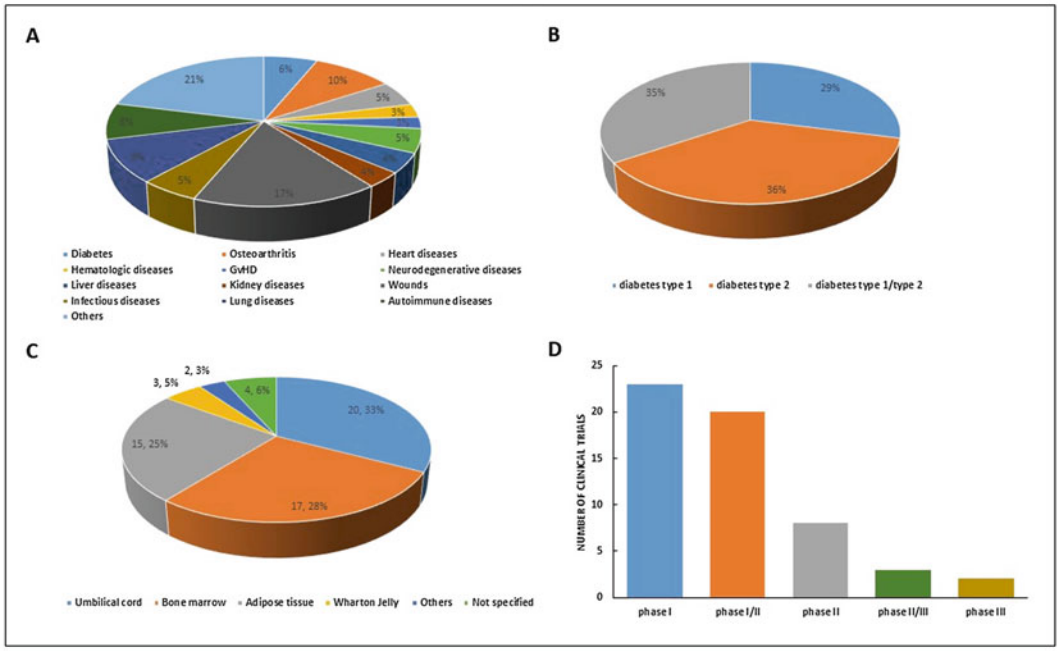

Fig. 2 Mesenchymal Stem Cell (MSC) clinical trials collected from clinicaltrial.gov from 2010 to August 2020 with the term "mesenchymal" listed 1,008 trials. (**A**) Percentages of MSC-based trials by disease classification, including diabetes (6%). (**B**) MSC human trials for diabetes are divided between diabetes type 1 (29%) and type 2 (36%). (**C**) MSCs used for diabetes are isolated from umbilical cord (33%), bone marrow (28%), adipose tissue (25%) and others (14%). (**D**) The majority of these MSC-based diabetes clinical trials are in Phase I (23 trials) and phase I/II (20 trials)

without immunosuppression plus Vitamin D supplementation in patients with early-onset T1D (Araujo et al. 2020). After 3-month follow up, the intervention group showed C-peptide stability, better glycaemic control and lower insulin requirement when compared to the control group with standard insulin therapy (Araujo et al. 2020). However, mild and transient adverse effects were reported in patients 3 months after AD-MSC infusion (Araujo et al. 2020).

Pancreatic beta cell dysfunction is a hallmark of T2D. Despite pharmacological treatment, this process is irreversible. Therefore, there is an utmost need for alternative therapies to restore β-cell function and optimize glycaemia; thus, preventing the occurrence of diabetic complications (Hinnen 2015). Many clinical studies have shown promising results utilizing MSCs for treatment of patients with T2D. Here, we present some of these trials registered in the ClinicalTrials.gov database. In a clinical study (NCT01413035) conducted by Kong et al., 18 patients with T2D were transfused intravenously with UC-MSCs (Kong et al. 2014). Six months later, UC-MSC transfusion effectively ameliorated hyperglycaemia and increased C-peptide levels in patients. Of note, the treatment was well tolerated with only 4 subjects reporting transient slight fever (Kong et al. 2014). A similar study (NCT01759823) was performed to assess the safety and efficacy of autologous BM-MSCs transplantation in 7 T2D patients (Bhansali et al. 2017). At 6 months, 6 out of 7 patients demonstrated reduction in insulin requirement by more than 50% from the baseline, while maintaining HbA1c < 7.0%, accompanied by improvement in beta cell function (Bhansali et al. 2017). Skyler et la also showed that single infusion of allogenic BM-MSCs was safe and feasible for a short period of 3 months in subjects

with T2D (NCT01576328) (Skyler et al. 2015). In another study (NCT01954147), treatment with UC-MSCs was investigated in T2D patients. Chen et al. showed that multiple infusions with UC-MSCs improved glucose metabolism and β cell function in patients diagnosed with T2D for more than 10 years (Chen et al. 2016).

As shown above, most clinical trials have indicated that treatment with MSCs from different sources are relatively safe and effective for both T1D and T2D. However, it is worth mentioning that the above studies have some limitations including the small sample size and short duration of treatment that should be addressed to assess long-term safety and efficacy. Moreover, before the widespread clinical application of MSCs for diabetes treatment, many challenges remain to be overcome such as the most suitable source, dose and route of MSCs for clinical effectiveness. Another critical issue is the cost-effectiveness and scalable generation of MSCs for medical application.

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