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THERAPEUTIC OF MESENCHYMAL STEM CELLS IN DIABETES

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ABSTRACT
This study aims to explain and analyze the effective treatment of diabetes mellitus by Mesenchymal Stem Cells with respect to traditional therapy based on oral anti-diabetic drugs. As well as to study its regularly consistent properties. The method used in this research is the case study method. Patient care records were the main source of data for this study including evaluation and analysis. So that the results of the study explain that at the same time the utilized products cultured by "CELLTECH STEM CELL LAB. and BANKING" as an integrated part of the Clinic, also get quality assurance. Effectiveness and efficiency including endogenous beta cell regeneration of pancreatic islets, and other therapeutic issues are novel and belong to cutting-edge treatment. Treatments performed at the Vinski Regenerative Stem Cell Main Clinic have shown positive research results. This has strengthened the level of trust in the clinic's medical services.

Keyword: therapeutic, diabetes, mcs.

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INTRODUCTION

Therapeutic of Mesenchymal Stem Cells in Diabetes

In recent years, diabetes mellitus has become one of the biggest health problems in the whole world (S. Gao et al., 2022). It was estimated that approximately 463 million adults worldwide suffer from diabetes in 2019, while it is estimated that by 2030 there will be 578 million people with diabetes (Saeedi et al., 2019). Diabetes is a major risk factor for stroke and ischemic heart disease, which together represent high rates of mortality and morbidity in adult patients (Lozano et al., 2012). Diabetes is also the leading cause of blindness and chronic kidney disease in adults (Garofalo et al., 2015); (Esteves et al., 2008). For the prevention of diabetes complications, improving glycemic control is essential. Type 2 diabetes mellitus (DMT2) accounts for 90% to 95% of diabetes mellitus cases. DMT2 occurs as a result of a combination of dysfunction of insulin-producing pancreatic beta cells and insulin resistance (Raz et al., 2013). Initial treatment of DMT2 generally involves oral antidiabetic drugs. However, over time, insulin becomes necessary for glycemic control as the disease progresses. Currently, available therapeutic regimens can improve hyperglycemia and temporarily improve insulin sensitivity in target organs. However, these treatments cannot reverse insulin resistance as well as disease progression and pancreatic beta cell dysfunction (Inzucchi, 2002).

However, none of the available therapies modulate the course of the disease. Animal studies have shown that glucagon-like peptide 1 (GLP 1) receptor agonists and dipeptidyl peptidase IV (DPP IV) inhibitors lead to improved pancreatic beta cell function. However, the improvement of beta cell function has not been confirmed in humans (Sasaki et al., 2015); (H. Y. Kim et al., 2014). Ideal therapy

options for DMT2 may be strategies to improve peripheral insulin resistance while promoting pancreatic beta cell regeneration (Zang et al., 2017). Cell-based therapies have emerged as next-generation drugs to address the complex pathophysiology of DMT2 (Volarevic et al., 2011); (Cho et al., 2018); (Domínguez-Bendala et al., 2012). Mesenchymal stem cells (MSCs) have shown therapeutic effects in animal studies as well as in clinical studies, opening the door to new methods for treating DMT2. MSCs could self-renew and differentiate into mesenchymal lineages, such as hydrogenic, adipogenic, and osteogenic lineages in vitro. MSCs show low immunogenicity due to moderate expression of major histocompatibility complex (MHC) class I and the absence of MHC class III as well as costimulatory molecules on the cell surface (Y.-L. Si et al., 2011) (Yi Zhang et al., 2014). In addition, a variety of growth factors, cytokines, and exosomes secreted by MSCs play an essential role in the regulation of insulin sensitivity as well as pancreatic beta-cell dysfunction (Sivanathan et al., 2015); (Su et al., 2019). Previous studies have shown that MSCs could exert certain anti-diabetic effects, which is supported by evidence that multiple infusions of MSCs can reverse hyperglycemia instead of a single infusion (Hao et al., 2013); (R. Jiang et al., 2011). This study aims to explain and analyze the effective treatment of diabetes mellitus by Mesenchymal Stem Cells with respect to traditional therapy based on oral anti-diabetic drugs. As well as to study its regularly consistent properties.

METHOD

Patient's data are collected regularly and recorded in the patient's notation book regarding the personal data and medical history. Since stem cells can be utilized for almost all medical follow up complaints, the use of stem cells is commonly based on the patient's own selection.

a. There are options to use the stem cell or other other kind of treatment handlings.
b. Stem cells consist of living cells which are maintained and cared for in "CELLTECH STEM CELL and BANKING Laboratory" in a "cryo tank" with a temperature of -1900C (below zero Celsius degree), carried out by "close system" or "open system".
c. Both conditions are owned by "Celltech Stem Cell and Banking Laboratory. The main concentration still relies on the source from Umbilical Cord and Umbilical Cord Blood.
d. Closed System is also called a quantum process. These two methods are implemented at the CELLTECH STEM CELL Laboratory." Stem cells are stored in vials containing 20 million cells or more. The closed system is more efficient and sterile because it runs automatically and quickly, in a well closed system away from human interventions.
e. A closed system is also known as a "quantum stem cell".
f. Provisioning is related to the type and severity of disease and the quantity of cells that is required.

Dosis

a. Based on the patient's body weight multiplied by 1 million cells, is the requirements dosis basically used. For a body weight e.g.of 70 kg, (1 X 70 million) cells are required. The allogeneic trait of stem cells opens the possibility to replace or increase the number of cells and regenerate to restore the number of damaged cells. Its allogeneic properties can replace any cell in the target location of recovery. The dose obviously depends on the number of damaged cells and replacing it. In general, a package of 20 million cells is minimally effective. More may be needed for more severe conditions.

b. In general, at least 6 months later, an inspection of its condition and effectiveness needs to be carried out
c. On this occasion, treatment for diseases such as Praderwili syndrome, and Autism, as well as other several others, have been
d. successfully treated.

RESULT AND DUSCUSSION

Mesenchymal Stem Cells

Mesenchymal stem cells are pluripotent progenitor cells that can differentiate into osteoblasts, adipocytes, chondrocytes, and other cell types of mesodermal origin (N. Kim & Cho, 2013). These cells have a high ability for self-renewal, the ability of immunological regulation, low immunogenicity, and have an essential role in clinical cell therapy. MSCs originate from different sources and were first isolated from bone marrow (Vining & Mooney, 2017). Research has since shown that MSCs can be isolated from various human tissues such as urine, menstrual blood, gingiva, synovium, umbilical cord, and adipose tissue (Packer, 2018); (Kasoju et al., 2017). MSCs are good for transplantation due to their low immunogenicity. After transplantation, MSCs can chemoattract near damaged tissues and secrete various anti-inflammatory and growth factors to promote the repair of damaged tissues (Jadalannagari & Aljitawi, 2015). However, mesenchymal tumor cells and MSCs have many identical phenotypes of stem genes, suggesting that some early tumor cells originate from MSCs (Galie et al., 2008). The clinical application of MSCs has been limited by factors revealed in studies showing that MSCs promote tumorigenesis through immunological regulation, vascularization, and the promotion of tumor interstitial remodeling (Yu et al., 2008); (Bagley et al., 2009). However, it was discovered that exosomes extracted from an MSC culture medium have a repair function like MSCs and do not have the risk of tumor formation (Timmers et al., 2008); (Cosenza et al., 2018).

MSCs are the most used stem cells in the human body because they have been easily isolated for many years. Since 2012, MSCs have been used clinically to treat various diseases such as Crohn's disease, graft-versus-host disease, and knee osteoarthritis. Type 1 diabetes mellitus is an autoimmune disease where immune cells attack the beta cells of the pancreatic islets of Langerhans. However, type 2 diabetes mellitus is thought to be a disease associated with insulin resistance, although recent research has shown that the disease is associated with immunological dysfunction. Therefore, MSC therapy may be a useful treatment for type 1 and type 2 diabetes mellitus. In preclinical studies as well as clinical studies, MSC transplantation in diabetic patients has shown significant improvement in diabetes with no adverse effects (Dang et al., 2017).

The Mechanisms of MSC Therapy

Therapeutic efficacy for DMT2 was hypothesized decades ago. However, the mechanisms of MSCs have not yet been fully elucidated. Therefore, several potential mechanisms of MSCs in DMT2 are described here (S. Gao et al., 2022).

Pancreatic Beta Cells Regeneration

MSCs promote insulin production, which facilitates the regeneration of endogenous beta cells of pancreatic islets. Previous studies have shown that MSCs can differentiate into beta cells or insulin-producing cells in vitro (El-Sherbiny et al., 2020); (Ghoneim et al., 2020); (L.-B. Chen et al.,

2004). In addition, a growing body of evidence suggests that limited transdifferentiation of infused MSCs can occur in vivo to facilitate the process of pancreatic regeneration as well as ameliorate hyperglycemia in DMT2 models (S. Gao et al., 2022). In mice, in addition to streptozotocin-induced increased insulin production 42 days after intravenous hBM-MSC injection, many transplanted cells migrated into ductal structures as well as islet structures, while only a minority of transplanted cells were labeled with insulin (Hess et al., 2003). MSCs can stimulate beta cell proliferation and trigger endogenous insulin production, transdifferentiation of MSCs into beta cells and transplant engraftment may not significantly contribute to pancreatic function restoration (S. Gao et al., 2022).

MSCs have shown the potential for repair through the secretion of various cytokines and growth factors, including interleukin 6 (IL6), transforming growth factor β (TGF-β), and vascular endothelial growth factor (VEGF), which participate through autocrine and paracrine action. to lead to the improvement of islet function (Caplan & Dennis, 2006) as well as the facilitation of the vascularization process (Park et al., 2010). Some studies have linked the potential of MSCs for islet repair to the apoptotic effects of MSCs. It has been demonstrated that BM-MSCs can reduce islet cell apoptosis because reduced caspase 3 cleavage in vivo was observed after MSC treatment (Borg et al., 2014). In addition, the anti-apoptotic effect of MSCs was proven in a study where the regulation of reactive oxygen species (ROS) was reduced, as well as superoxide ions, nitric oxide, caspase 8, caspase 3, and p53, as well as the regulation of Bcl2 under hypoxic conditions (Chandravanshi & Bhonde, 2017). BM-MSCs could attenuate endoplasmic reticulum stress-induced apoptosis by Myc overexpression via cell-cell interaction or stromal cell factor 1 (He et al., 2018).

In addition, MSCs can also enhance the formation of autophagosomes by cleaning damaged mitochondria and increasing insulin secretion (K. Zhao et al., 2015). Mitochondria are essential for energy production, cell apoptosis, and signaling, and their function is important in many diseases such as ischemia, diabetes, aging, and inflammation. Studies have shown that MSC-mediated mitochondrial transfer is essential support for rescuing injured cells and restoring mitochondrial function (Yuan et al., 2021); (Gomzikova et al., 2021). MSC mitochondria can be transferred to beta cells when under hypoxic conditions for replenishment (Rackham et al., 2020). Therefore, the rate of insulin secretion, as well as the rate of oxygen consumption in islet cells, are improved after culturing with MSCs. This indicates that mitochondrial transfer can potentially respond to and alleviate oxidative and hypoxic stress resulting from excessive ROS production in damaged mitochondria (Rackham et al., 2020). Mitochondria have an essential role in energy metabolism, and therefore their intercellular transfer can partially explain the therapeutic mechanism of MSCs in improving the regeneration of beta cells. In addition, studies have postulated that the donation of mitochondria by MSCs can prevent other complications that occur in diabetes, such as inflammation and diabetic nephropathy (Konari et al., 2019); (Planat-Benard et al., 2021); (Yuan et al., 2021).

MSC for Alleviation of Insulin Resistance

Insulin resistance is a hallmark of DMT2 and describes the failure of cells to respond to insulin during disease progression. Intravenous injection of BM-MSCs increases GLUT expression and upregulates insulin receptor substrate 1 (IRS-1) phosphorylation as well as AKT in insulin target tissues (Y. Si et al., 2012). This suggests that MSCs could alleviate insulin resistance in T2DM patients (Si et al., 2012). MSCs inhibit the E3 ligase Mitsugumin 53 (MG53) which promotes ubiquitinoylation of IRS-1 in skeletal muscle (Wei et al., 2008). Skeletal muscle accounts for 70% to 80% of insulin-

stimulated glucose disposal, while inhibition of the IRS-1 ubiquitin pathway may be key to alleviating insulin resistance (Shulman et al., 1990). Insulin resistance in Metabolic Dysfunction-Associated Fatty Liver Disease (MAFLD) and other subsequent liver diseases is associated with excessive production of inflammatory mediators as well as their downstream signaling molecules. Here, evidence suggests that the NOD-like receptor protein 3 (NLRP3) inflammasome plays an essential role in obesity-induced insulin resistance (Esser et al., 2014). MSCs applied for the treatment of DMT2 showed that the formation of NLRP3 was inhibited through the regulation of the immune response of MSCs, leading to the improvement of GLUT4 and IRS-1 function in liver cells (Sun et al., 2017).

Exosomes are extracellular vesicles on the nanoscale and have the potential for tissue regeneration and damage repair. In vivo experiments showed the therapeutic effects of intravenously injected MSC exosomes on reducing blood glucose levels and restoring IRS-1 phosphorylation as well as AKT signaling pathways in insulin target tissues (Sun et al., 2017). It has been confirmed that exosomal miR-29b-3p can regulate cellular insulin sensitivity with the help of sirtuin-1 (Su et al., 2019), which is a class III histone deacetylase deeply involved in the regulation of genomic stability, apoptosis, and gene expression. This suggests that histone modification associated with insulin resistance is a potential treatment approach for MSCs. In addition, insulin resistance can be improved by reducing ROS< removal of dysfunctional mitochondria as well as alleviating endoplasmic reticulum stress (Bi et al., 2018).

Hepatic Metabolic Homeostasis and MSCs

DMT2 is associated with liver dysfunction where approximately 57% to 80% of baboons suffering from DMT2 also suffer from MAFLD. The relationship between DMT2 and MAFLD is bidirectional and complex because the characteristics and metabolic syndromes are similar, such as glucose tolerance, oxidative stress, and lipid accumulation in the liver (Anstee et al., 2013). Intravenous MSC therapy can lead to a significant reduction in a panel of biochemical markers of liver function disorders caused by a high-fat diet, such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), and alkaline phosphatase (AKP). This suggests that MSCs can improve liver function in DMT2 patients (Ezquer et al., 2011). The main regulators of lipid metabolism are PPARs, which help control fatty acid balance, beta-oxidation, and adipogenesis. In mice on a high-fat diet, after the introduction of MSC, PPAR-alpha was increased while PPAR-gamma was decreased in the liver. This suggests that the PPAR signaling pathway is modulated by MSCs, which has an impact on liver metabolism (C.-W. Lee et al., 2017).

Oxidative stress caused by mitochondrial dysfunction leads to a metabolic imbalance in the liver (Wei et al., 2008). The glutathione/oxidative glutathione (GSH/GSSG) ratio was decreased, while the amount of superoxide dismutase, inversely proportional to systemic ROS levels, was increased after MSC treatment (W. Jiang et al., 2018); (Ho et al., 2012). This leads to the assumption that MSC therapeutic effect is largely related to metabolic homeostasis. Treatment with MSC conditioned medium showed similar effects, indicating that paracrine effects have a significant contribution to the repair process in DMT2 (Nagaishi et al., 2014). Intravenously injected MSC resides in the liver for five days after administration and remains in the liver for 15 days after treatment. Bioactive factors such as APOM and IGFBP2 secreted by MSCs paracrine increase insulin sensitivity and reduce lipid accumulation in hepatocytes via PI3K-AKT activation (Yuanyuan Zhang et al., 2021).

Regulation of Systemic Inflammation and MSCs

The pathogenesis of insulin resistance is associated with obesity, where chronic low-grade inflammation and activation of the immune system are involved (Esser et al., 2014). Overexpression of inflammatory cytokines such as IL1β, IL6, and TNF-α is therefore associated with the pathogenesis of metabolic syndromes including MAFLD, atherosclerosis, and insulin resistance. Abnormal changes in tissue and peripheral immune cells as well as their regulatory function always accompany the development of diabetes, which suggests that immune cells such as T cells, natural killer cells, and macrophages simultaneously participate in the progression of DMT2 (Esser et al., 2014). MSCs have an immunomodulatory effect on B lymphocytes, T cells, natural killer cells, and dendritic cells through para-kinetic effects that include the secretion of extracellular vesicles, growth factors, anti-inflammatory mediators, cytokines, chemokines, and enzymes (J. Chen et al., 2021); (Hashemian et al., 2015). MSC activation is subject to stimulation by many inflammatory cytokines, including interferon-γ (INF-γ) and TNF-α, which switch to an immunosuppressive phenotype inducing the secretion of soluble factors that mediate immunomodulatory activities such as IL10, indoleamine-pyrrole 2,3-dioxygenase (IDO, hepatocyte growth factor (HGF), and prostaglandin E2 (PGE2) (Shrestha et al., 2021); (F. Gao et al., 2016). The paracrine immunomodulatory properties of MSCs are mediated by different signaling pathways such as the Rap1/NF-κB pathway (Ding et al., 2018). However, until now, the precise mechanism of MSC-based immunomodulation is not fully understood, although MSCs are used to treat immune-mediated disorders(Ma et al., 2014) (Singer & Caplan, 2011) which includes diabetes (S. Gao et al., 2022).

The results of experiments carried out so far have shown in an animal model with diabetes that the inflammatory status contributes to the modification of the pancreatic microenvironment, and MSC treatment promotes the proliferation of regulatory T cells to ensure long-term immunoregulatory effects (Boumaza et al., 2009). Th2 cytokines (IL13 and IL10) secreted by regulatory T cells seem to play an essential role in the survival and activation of beta cells through anti-inflammatory effects, where the definitive mechanism of action is still unknown (Anne-Marie Madec et al., 2009). Mobilization of MSCs by inflammatory factors in specific microenvironments has been demonstrated, indicating that MSCs can induce the switch of macrophages to an anti-inflammatory phenotype to alleviate insulin resistance in DMT2 patients (Yin et al., 2018)(Z. Xie et al., 2016). Classically activated macrophages (M1) can stimulate MSCs to overexpress MCP-1 and IL6, which converts M1 to an alternatively activated M2 phenotype. In the meantime, the expression of IL-4R is enhanced in macrophages, which makes them sensitive to the IL4 stimulus. MSCs can reduce systemic inflammatory cytokines to impair the action of insulin receptors as well as the corresponding downstream signaling pathways by preventing the formation of NLRP3 in the liver and adipose tissue (Sun et al., 2017). TNF-α and IL-1β secreted by DMT2 islets can stimulate MSCs to secrete IL-1Ra, while this can potentially lead to attenuation of islet inflammation (L. Wang et al., 2020).

Efficacy and Safety of MSC Therapy in Patients with DMT2

A pilot study in China showed that transplantation of placenta derived MSCs in patients with long-term DMT2 is easy, safe, and potentially effective (R. Jiang et al., 2011). 10 patients with DMT2 whose duration was greater than or equal to three years participated in the research, glucose was poorly controlled in these patients, and they were dependent on insulin. The study participants were brought closer to real clinical conditions because they had comorbidities that often occur in

diabetics, such as vascular complications, kidney disease, and heart disease (R. Jiang et al., 2011). Patients received an average of 1.35 * 106 kg of placental stem cells during three separate treatments with one-month intervals between therapeutic infusions (R. Jiang et al., 2011). HbA1c and insulin dose measurements six months after MSC treatment showed a trend of improvement for all patients. After treatment with MSCs, the release of insulin and C-peptide was improved (R. Jiang et al., 2011). According to a meta-analysis (El-Badawy & El-Badri, 2016), patients with DMT2 may benefit from MSC therapy. Another meta-analysis (Li et al., 2021) also showed that patients with diabetes may benefit from MSC therapy. A meta-analysis (Li et al., 2021) included 10 studies with 239 patients with diabetes. Compared to percentile levels, there were significant changes in F-CP, PBG, FBG, HbA1C as well as insulin requirements in diabetic patients after MSC therapy (Li et al., 2021). Another analysis showed that MSC therapy has a role in glucose control in DMT2 patients (Ranjbaran et al., 2021).

In diabetic animals, human MSCs or islet-like cells derived from human MSCs have been successfully transplanted (Ho et al., 2012); (J. Kim et al., 2012). Transplantation of MSCs in animals with diabetes leads to a decrease in the level of glucose in the animals' blood. MSC infusion can improve blood glucose homeostasis in animals with DMT2 and DMT1. After infusion of MSCs, there was a reduction in blood glucose levels for several days to two weeks, where the reduction was sustained from 20 days to 10 weeks after treatment (Ho et al., 2012)(Ammar et al., 2015)(Zhou et al., 2015) (R. H. Lee et al., 2006). Glycemic effects can be improved by multiple MSC transplantations (R. H. Lee et al., 2006)(Ho et al., 2012). After seven administrations of MSC therapy, glucose levels are significantly normalized (Ho et al., 2012). Insulin-producing cells (IPCs) derived from MSCs are effective for the treatment of diabetes. MSC-derived IPC cells have many characteristics as true pancreatic beta cells including insulin production, C-peptide expression, pancreatic beta cell-specific gene expression, and the ability to respond to glucose (Seyedi et al., 2016)(Gabr et al., 2013)(Seyedi et al., 2016) (Dang et al., 2015). IPCs transplanted into the kidney capsule (Kadam et al., 2010); (Hu et al., 2012) and liver (Timmers et al., 2008) led to a decrease in glucose levels three days after treatment, while normalization occurred after more than nine weeks from treatment or until graft removal (Kadam et al., 2010) (Timmers et al., 2008) while some results showed that IPC transplantation did not lower glucose levels (Hu et al., 2012).

A meta-analysis (Rahim et al., 2018) that included 11 studies of stem cell therapy involving 363 T2DM patients showed that stem cell treatment improved HbA1C, and daily insulin requirements, and induced the specified variables. However, stem cell therapy had a negative effect on C-peptide (Rahim et al., 2018). A meta-analysis (Rahim et al., 2018) revealed 20 different reported adverse effects of stem cell therapy, where fever was the most frequently reported with an incidence rate of 0.14%. In addition, patients rarely reported contusion, muscle strain, hematuria, viral gastroenteritis as well as folliculitis complications, the incidence rate of which was 0.02% (Rahim et al., 2018). Another study (Mathur et al., 2023) showed that treating patients with DMT2 with MSC therapy led to a reduction in the dose of antidiabetic drugs over a period of 12 months. The effective dose of MSC therapy ranged from 1 * 106 cells/kg to 3.7 * 106 cells/kg (Mathur et al., 2023). After the treatment, the level of HbAc1 decreased by an average of 32%, while the level of glucose in the blood was reduced by an average of 45%. C-peptide levels in patients were reduced by 38% in two

trials and increased by 36% in four trials. No serious side effect (Mathur et al., 2023)s were noted in any of the trials (Mathur et al., 2023).

MSC Therapy for DMT2 Clinical Studies

DMT2 occurs because of inflammation and immunological dysfunction, which are most likely essential factors for the development of insulin resistance in this disease. MSC therapy is expected to effectively cure DMT2 as well as ameliorate insulin resistance in humans as was the case in animal studies (Huang et al., 2021)(H.-J. Kim et al., 2018)(M. Wang et al., 2018) (Deng et al., 2018). al., 2018). Studies published so far have confirmed that MSC therapy can effectively reduce HbA1c, PBG, and FBG, improve insulin resistance, and reduce insulin requirements. During the follow-up period, MSC therapy was shown to have a significant effect in clinical trials. Adverse effects that occurred because of MSC therapy in clinical trials are nausea, fever, vomiting, subcutaneous hematoma, minor hypoglycemia, and headache. However, all symptoms were alleviated after symptomatic treatment and without side effects and serious complications. However, previous studies have had a follow-up period of only 12 months, and therefore longer studies are needed to assess long-term complications and side effects. Although there are still many challenges, according to the current results, MSC therapy represents a potential method for DMT2 and promises new ways to treat diabetes (Huang et al., 2021).

The efficacy of MSCs for the treatment of DMT2 was demonstrated by the publication of a clinical study (A. Bhansali et al., 2009) where B-MSCs were used and transplanted into the pancreas of 10 patients suffering from DMT2. Patients were followed for six months after treatment (A. Bhansali et al., 2009). Seven out of 10 patients in the study reduced their insulin requirements by more than 50%, while of these seven, two patients were able to stop using insulin completely at day seven and day 41 after B-MSC therapy (A. Bhansali et al., 2009). In all patients, there was a significant reduction in the need for insulin, an increase in C-peptide, and an improvement in HbA1c (A. Bhansali et al., 2009). Subsequently, PD-MSCs were used in 10 patients in a pilot phase I clinical trial where patients were administered three separate intravenous doses of PD-MSCs at one-month intervals (R. Jiang et al., 2011). Follow-up tests were performed three months after the last MSC dose (R. Jiang et al., 2011). In all patients treated with PD-MSC, there was a significant decrease in HbA1c, a decrease in daily insulin doses, and an increase in C-peptide levels (R. Jiang et al., 2011).

A randomized, prospective, single-blind, and placebo-controlled study was conducted to evaluate the safety and efficacy of B-MSC therapy in patients with DMT2 (A. Bhansali et al., 2014). 21 patients participated in the research (A. Bhansali et al., 2014), of which 11 patients received B-MSC therapy, and 10 received placebo therapy. Additional tests were performed three, six, and 12 months after the end of treatment. There was a significant improvement in C-peptide levels and insulin dose between cases and controls (A. Bhansali et al., 2014). Insulin requirement after B-MSC therapy was reduced by more than 50% while HbA1c values were below 7% (A. Bhansali et al., 2014). Another placebo-randomized controlled trial (S. Bhansali et al., 2017)examined the efficacy of autologous BM-MSCs compared to bone marrow-derived mononuclear cells (BM-MNCs). 30 patients participated in the study, of which 10 received a placebo, 10 BM-MSC, and 10 patients were treated with BM-MNC (S. Bhansali et al., 2017). There was a significant reduction in daily insulin requirements in the BM-MSc group 12 months after the end of treatment. In the BM-MNC group, after 12 months, the daily need for insulin was reduced and there was a significant increase in C-

peptide levels (S. Bhansali et al., 2017). The reduction in daily insulin requirement was greater in patients from the BM-MNC group compared to patients from the BM-MSC group, while the BM-MNC group also showed increased sensitivity to insulin after treatment (S. Bhansali et al., 2017).

The described studies showed that transplantation of MSCs leads to the alleviation of the metabolic burdens that occur due to DMT2. The studies have shown that MSCs have the ability to significantly reduce daily insulin requirements (A. Bhansali et al., 2014); (S. Bhansali et al., 2017) (A. Bhansali et al., 2009); (R. Jiang et al., 2011), to reduce HbA1c levels (A. Bhansali et al., 2009); Jiang et al., 2011), as well as to increase C-peptide levels (A. Bhansali et al., 2009). However, further studies are needed to better understand the efficacy of this therapy, as well as the mechanisms through which MSC transplantation may lead to improvement in DMT2 patients (Cho et al., 2018). In a rat model of DMT2, MSC therapy leads to a reduction in blood glucose levels and effective mitigation of hyperglycemia (Hao et al., 2013) (M. Xie et al., 2017)(Z. Xie et al., 2016)(Y. Zhao et al., 2013) (Y. Si et al., 2012). Several mechanisms have been found to be involved in the reduction that occurs in patients with DMT2, including improved insulin sensitivity in peripheral tissues as well as the promotion of pancreatic beta cell function. Insulin sensitivity is thought to be improved as a result of increased GLUT4 expression as well as increased levels of phosphorylated IRS1 and AKT in target tissues. AKT and IRS1 represent part of the insulin signal transduction pathway to promote GLUT4 translocation and glucose uptake. The ability of MSCs to improve hyperglycemia may be short-lived because so far the reduced blood glucose levels have been transient after MSC treatment. A single infusion of MSCs leads to a reduction of hyperglycemia for four weeks, after which hyperglycemia returns to the state before MSC treatment (Y. Si et al., 2012).

Another trial (Hao et al., 2013) also showed that the effects of MSC therapy lasted only two to three weeks even after serial infusions of MSC therapy. Therefore, additional studies are needed to determine the sustainability of MSC treatment in DMT2 patients, as well as to clarify the exact mechanisms of MSC therapy. However, the downside of animal studies is that animal models do not reflect the true pathological state of DMT2 that occurs in humans (A. Bhansali et al., 2014). More human clinical studies are needed to determine the potential side effects of MSC treatments. In one study (A. Bhansali et al., 2009), side effects noted were nausea in six out of 10 patients and vomiting in one out of 10 patients. In two patients from the study (A. Bhansali et al., 2014), there was a sudden drop in hemoglobin that was corrected within a month. However, another study (R. Jiang et al., 2011) did not record any adverse effects of MSC therapy, while improving heart and kidney function after MSC therapy was observed. However, although minimal side effects were generally reported, clinical studies only followed patients for 12 months and involved only a small number of patients. Further studies are necessary that will include a larger population of patients, and a longer period of follow-up of patients after the end of treatment, to determine the efficacy and safety of MSC therapy in patients with DMT2. The individual outcomes of the studies conducted so far have given promising results. However, due to the different methodologies used in the studies, it is difficult to compare the obtained results (Cho et al., 2018).

Case Study

MSCs were cultured in the laboratory to develop islet cells. Four patients with T2DM participated in this case study. The average age of the patients was 62.5, of which two were women

and two were men. After MSC therapy, all patients experienced a decrease in blood glucose and HbA1c levels.

Table 1. HbA1c in patients with DMT2 after MSC therapy

Patient	Age	Sex	HbA1c (1) %	HbA1c (2) %	HbA1c (3) %
A	68	Female	6.4	6.1	
B	56	Male	6.4	5.7	
C	56	Male	5.8	5.7	5.5
D	70	Female	8.5	7.5	

Table 2. Glucose levels after MSC therapy

Patient	Age	Sex	Glucose (1) mg/dL	Glucose (2) mg/dL	Glucose (3) mg/dL
A	68	Female	107	96	
B	56	Male	107	95	
C	56	Male	95	89	82
D	70	Female	189	173	

Risks of Intravenous Administration of MSC Therapy

The therapeutic effects of MSCs are greatly influenced by the delivery route of MSC therapy. The most frequently used way of introducing MSC therapy in clinical studies and research with animals is intravenous injection. A bioluminescence system is used to monitor the in vivo biodistribution of MSCs. Impoverished cell survival was activated after the majority of MSCs were trapped in pulmonary capillaries and were eliminated within a few hours after injection in the tail vein of mice (Schrepfer et al., 2007). However, during long-term follow-up, the fluorescence signal in the lungs gradually disappeared, and therefore the fate of MSCs in the lungs is controversial (de Witte et al., 2018). As a potential safety issue in cellular therapies, microthrombi occur due to blockages of the pulmonary capillaries. Intravenous infusion of MSCs leads to a decrease in the blood flow rate in the pulmonary capillaries, which can lead to the formation of thrombus in the blood vessels (Mäkelä et al., 2015). To address this issue, heparin was mixed with the cell suspension during systemic injection (Liao et al., 2017). In addition, MSCs were treated with a hypertonic solution before introduction to reduce cell size (Leibacher et al., 2017). There are suggestions that the size of MSCs will gradually increase with extended passage of culture (Leibacher et al., 2017), and this suggests that infusion of low-passage MSCs will reduce microthrombi formation (S. Gao et al., 2022).

Numerous adverse effects of MSC therapy in DMT2 patients have been reported in previous studies. Some even unwanted events can be interpreted because of disease progression after cell therapy that did not have a sufficient therapeutic effect. In three patients with age-related macular degeneration, vision loss occurred as a negative reaction to adipose-derived MSC therapy (Kuriyan et al., 2017). MSC therapy in another study did not by itself lead to full-thickness recovery of ulcerated skin after it was applied topically (Maksimova et al., 2022); (Baranovskii et al., 2022). The benefit-risk ratio and patient safety are the most important factors in clinical practice. Therefore, all adverse events are monitored in clinical trials with DMT2 patients and MSC treatment. Potential risks of MSC therapy include adverse events in the upper respiratory tract and lungs (intravenous injection causing infused cells to pass through the lungs), acute immunological and allergic adverse events, as well as the formation of unwanted tissue and injury caused by the puncture. Acute immunological and allergic adverse events were not (Estrada et al., 2008); (A. Bhansali et al., 2009); (A. Bhansali et

al., 2014); (Liu et al., 2014); (Hu et al., 2012); (Sood et al., 2015); (R. Jiang et al., 2011); (Kong et al., 2014); (Skyler et al., 2015); (Thom et al., 2006); (Wu et al., 2014); (Y. Zhao et al., 2013).

Although the formation of unwanted tissue was not found, it should be evaluated during long-term follow-up of patients. Studies (Wu et al., 2014); (A. Bhansali et al., 2009); (Liu et al., 2014) reported a low incidence of punctate hemorrhage, subcutaneous injection site hematoma, and post-traumatic pain after MSC transplantation, respectively. Moderate and relapsing fever with spontaneous remission after transvenous MSC transplantation has been reported in 13.6% to 22.2% of patients (Kong et al., 2014); (Liu et al., 2014). After MSC transplantation, patients experienced transient self-limiting nausea, headache, vomiting, upper respiratory tract infection, and abdominal pain (A. Bhansali et al., 2009); (Skyler et al., 2015); (Liu et al., 2014). Low hypoglycemia occurred frequently in patients who continued to use antidiabetic drugs after MSC therapy, while severe hypoglycemia was not reported (Zang et al., 2017).

CONCLUSION

This study confirms the trust on the therapeutic power of stem cells for diabetes mellitus and strongly provided consistent traits on other dysfunctions with Prader-Willi syndrome and autism tests conducted in the previous quarter before. Another opportunity gained with this study was the support of the quantum closed system machine that successfully cultivated the healthy stem cell product outputs to be applied to this study. Based on the results of this study, the management of the clinic decided to escalate the capacity and quality of the stem cell culture machines and the experts of manpower in the near future.

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