Annals of Clinical Cases

ISSN: 2692-7993

Mini Review

Mesenchymal Stem Cells for Type 1 Diabetes Treatment - A Review Article

Rim M. Harfouch[1], Hrag Torossian[2] and Hala Qabalan[1]*

[1]Department of Microbiology and Biochemistry, Al Andalus University, Tartous, Syria

[2]Faculty of Medicine, Yervan State Medical University, Yervan, Armenia

Abstract

Type 1 Diabetes Mellitus (T1DM) is characterized by beta cells destruction therefore, the disability of producing insulin. It is well known how difficult it is for T1DM patients to take their daily insulin injections to maintain the glucose levels stable. But one method has the highest potential capability of succeeding which is the transplantation of pancreatic islets of Langerhans. Newly introduced methods lead to an obvious decrease in the concerns related to embryonic or induced pluripotent stem cells for T1DM therapy. One of these methods is using Mesenchymal Stem Cells (MSCs). MSCs are derived from different tissues such as bone marrow, adipose tissue, nervous tissue, umbilical cord, amniotic fluid, placenta and dental pulps. They have the ability to differentiate into lines of mesenchymal tissues including bone, fat, and cartilage.

The transplantation procedure of MSCs can theoretically lead to an increase in beta cell mass via the following effects: (1) Changing the local microenvironment by production of chemokines, cytokines and factors to stimulate regeneration; (2) Decrease or prevention of autoimmunity against beta cells; (3) Replacement of beta cells through *in vitro* or *in vivo* differentiation.

Keywords: Mesenchymal stem cells (MSCs); Type 1 diabetes mellitus (T1DM); Transplantation

Introduction

Type 1 Diabetes Mellitus (T1DM) is characterized by beta cells destruction therefore, the disability of producing insulin. It is well known how difficult it is for T1DM patients to take their daily insulin injections to maintain the glucose levels stable, or to adapt with the modern techniques such as insulin pumps that can't guarantee total recovery and an easy way of life, as well as the long term complications of these treatments [1].

Despite all of this, one method has the highest potential capability of succeeding which is the transplantation of pancreatic islets of Langerhans. This kind of therapy stays limited by numerous factors, such as the lack of donor pancreases [2].

Either the whole pancreas or pancreatic islets have been transplanted in clinical experimental trials. The first whole pancreas transplantation was performed in the 1960s and became more common in the 1980s. On the other hand, islet transplantation in the 1970s depended on islets derived from animal models and were effectively transplanted without the need of major surgery. Islet transplantation was first clinically used to treat human type I diabetes patients in 1989 [3].

Citation: Harfouch RM, Torossian H, Qabalan H. Mesenchymal Stem Cells for Type 1 Diabetes Treatment - A Review Article. Ann Clin Cases. 2021; 2(1): 1025.

Publisher Name: Medtext Publications LLC

Manuscript compiled: Jan 13th, 2021

***Corresponding author:** Rim M. Harfouch, Department of Microbiology and Biochemistry, Faculty of Pharmacy, Al Andalus University, Tartous, Syria, Tel: 00963932292303; E-mail: rimharfouch@au.edu.sy

Islet transplantation: difficulties and challenges

At the times of introducing the first pancreatic islet transplantation in the 1980s, less than 10% of the treated patients remained insulin independent only for 1 year. But this percentage increased in the 2000s when Edmonton tested new steroid-free immunosuppressive drugs on seven patients in a medical trial and all of them achieved insulin independence at first year.

There are two known sources for pancreatic islets, one from the patient's own pancreas (autotransplantation), and the other from a diseased donor's islets (allotransplantation). Islet autotransplantation is performed on chronic pancreatitis patients using islets extracted from their own pancreas as a means of preventing from later occurrence of diabetes [4].

Islet allotransplantation begins with selecting the appropriate pancreas from deceased donors, followed by the extraction, isolation, and purification of islets. The transplantation outcomes are affected by donor related factors such as: age, body mass index and the cause of death (cardiac or brain death) in addition to the duration of the ischemic cold storage [5].

Difficulties of islet transplantation

While the duration of the ischemic cold storage presents itself as a crucial factor of the transplantation outcomes, its ability of improving the quality of islets used for transplantation is still unexplained.

In the early days of islet transplantation, the reasons of graft failure were unclear and confounded by the toxic β-cell immunosuppressive agents. Many studies proved that ischemic cold procedures with duration of more than 8 hours might result in a decrease in islet yield. One way of avoiding such damage, is by keeping the procured pancreas in a solution containing high percentage of oxygen [6].

On the other hand, there are other difficulties related to the pancreas transplantations, such as the differences between the rates of diseased donors and recipients. Donors over 50 years are unsuitable to

donate for transplantation according to some centers.

There are other pancreas related, like organ damage during the organ removal procedure, arterial damage, fatty appearance of pancreas (pancreatitis), lack of islets and all of these factors can lead to organ discard, which decreases the chance of successful transplantation. For example, in the UK less than 50% of patients proceed to transplantation [7].

Characteristics of MSCs

Newly introduced methods lead to an obvious decrease in the concerns related to embryonic or induced pluripotent stem cells for T1DM therapy. One of these methods is using Mesenchymal Stem Cells (MSCs).

Many researchers have been conducted on different types of stem cells, but scientists preferred utilizing MSCs because they can be isolated from many different sources like placenta, navel cord blood, cartilage and bone marrow. MSCs have many advantages over other types of stem cells; they are multipotent and have regenerative, low immunogenicity and high immunomodulatory properties. Unlike embryonic stem cells, MSCs do not face any ethical problems [8].

History

Since the first discovery of bone marrow stromal cells by friedenstein et al. [9] in 1968 they were identified as adherent, fibroblast like populations in adult bone marrow and capable of differentiating into other cells of mesenchymal linage such as fat and cartilage. In 1991 Caplan was the first to name them Mesenchymal Stem Cells (MSCs) to refer to their multipotent properties [10].

Properties

An early study valuating the function of MSC *in vivo* explained systemic infusion of allogeneic bone marrow derived from animals. After adding host MSCs, Nauta et al. demonstrated the occurrence of significant long-term engraftment enhancements associated with endurance to donor and host antigens [11].

MSCs are derived from different tissues such as bone marrow, adipose tissue, nervous tissue, umbilical cord, amniotic fluid, placenta and dental pulps. They have the ability to differentiate into lines of mesenchymal tissues including bone, fat, and cartilage Unproved suggestions claim that these cells can differentiate into other types of tissues and including cardiomyocytes, lung epithelial cells, neurons, hepatocytes, and pancreatic islets [12,13].

MSCs transplantation can theoretically increase beta cell mass via the following effects: (1) beta cell replacement through *in vitro* or *in vivo* differentiation; (2) local microenvironment modification by production of cytokines, chemokines and factors to stimulate endogenous regeneration; (3) reduction or prevention of autoimmunity to beta cells [14]. Although several MSC transplantation studies have clearly shown the outcome of controlled glucose metabolism, there have been observations of decreased insulin resistance as well as enhanced beta cell function effects. Moreover, the mechanisms of MSC treatment of T2DM still not well understood. Some studies have suggested that the immunomodulatory and inflammatory effects of MSCs are what contribute to the resulting reduction of insulin resistance [15,16].

MSC's transplantation

The most commonly isolated MSCs are from bone marrow, where bone marrow aspirates are gradient centrifuged to isolate mononuclear cells, followed by *in vitro* culture. Although MSC preparations generated ex vivo appear homogenous under the light microscope, they probably compromise a heterogeneous group of progenitor cells and, on most occasions, do not fulfill strict criteria for a stem-cell entity at a single cell level (i.e., self-renewal and multi-linage differentiation capacity) [12].

Kerby et al. assessed the role of alginate encapsulation and co-transplantation of mouse islets and kidney MSCs *in vitro*. Only capsulated islets or duo-encapsulated with MSCs (islet+MSC) were transplanted into diabetic mice intraperitoneally, and blood glucose concentrations were monitored. They demonstrated that islets co-encapsulated with MSCs *in vitro* had increased glucose-stimulated insulin secretion.

After six weeks 71% of the co-encapsulated mice were cured compared with 16% of the islet-alone group [17].

In vitro coordinated trans-differentiation of MSCs into Insulin Producing Cells (IPCs) revealed that IPCs can be created from unconstrained differentiation utilizing Embryonic Stem Cells (ESCs). In spite of the fact that the quantity of IPCs and the insulin content in these cells was low, it was the main evidence which demonstrated that foundational micro organelles of ESCs were a potential hotspot for producing β-like cells. MSCs can be effortlessly acquired and are effectively extended and refined in the research facility. Diverse sorts of undeveloped cells require distinctive culture and enlistment media for trans-differentiation of IPCs to occur. The limit of MSCs to experience utilitarian trans-differentiation has been addressed throughout the years. In any case, ongoing investigations show that quality treatment or factor-based trans-differentiation of MSCs is two particular pathways to be considered as methods for getting useful β-cells.

Gene therapy allows the *in vivo* or *in vitro* exchange of an external gene into MSCs, enabling it to produce insulin. With that in mind, the quality of these genes initiates or curbs on request the insulin efficacy. The factor-based approach includes presenting MSCs to a mixture of insulin-advancing variables and cytokines over a broadened time of *in vitro* culture, trailed by transplantation of the trans-differentiated IPCs into the receiving diabetic patient. MSCs can be separated into IPCs by utilizing a particular culture medium enhanced with extraneous insulin-advancing variables. The IPCs trans-differentiation period changes significantly with the utilization of various conventions, it might last from a few to several days.

Cautious utilization of serum and glucose in the acceptance media has likewise been shown for effective trans-differentiation of IPCs. Motioning by these elements in MSCs permits the acceptance of the translation factors, which are requirements for pancreas improvement [18].

Most MSC's studies were carried out on rat models, until Vanikar et al. [19] 2010 tested the co-transplantation of adipose tissue derived Insulin-Secreting Mesenchymal Stem Cells (IS-AD-MSC) and Cultured Bone Marrow (CBM) for 11 T1DM patients as insulin replacement therapy. In this study cell cocktail was transplanted per omental cannulation by mini-laparotomy and cells were infused. After that, blood sugar levels were monitored after transplantation every 4 hours for 3 days, then 12 hourly for one week. All patients had successful co-transplantation without any adverse effects, and all of them had decreased exogenous insulin intake and became free of ketoacidosis events.

Therapy comparison: BM-MSC's and UC-MSCs

There are many other types of cells used in treating T1DM, but we concentrated on the use of Umbilical Cord Mesenchymal Stem Cells [UC-MSCs] and Bone Marrow Mesenchymal Stem Cells [BM-MSCs].

Therapy using BM-MSCs; One open, single center, randomized pilot study took place in Uppsala University Hospital on 9 patients. It aimed to the evaluation of safety using autologous MSCs in treating T1DM. The treatment efficacy has been evaluated and the assessments contained response of fasting C-peptide and evoked C-peptide to a Mixed-Meal Tolerance Test (MMTT), control of blood glucose by HbA1c, differences in insulin doses per kilogram, and differences in autoantibodies to β-cells levels (GAD65 and IA2 antibodies). At the one-year follow up, the values of the C-peptide reached a peak of nearly 12% and the Area Under the Curve (AUC) C-peptide peak was approximately 21%. In addition, through this 1st year, only 3 of the 9 patients treated with MSCs reduce their peak of AUC or C-peptide response to the MMTT. No differences were noticed in the hesitancy of GAD65 or IA2 antibodies. In summary; the patients which were randomized for MSC treatment had a grow in their capacity for the response of C-peptide to the MMTT, in addition to increased delta values for the peak response of C-peptide and AUC C-peptide to the MMTT [20].

Considering UC-MSCs, Hu et al. [21] conducted a double blind study which aimed to the assessment of long term effects of the plantation of mesenchymal stem cells derived from Warton's Jelly (WJ-MSCs) from the umbilical cord for T1DM treatment. The function of pancreatic β-cell was assessed by the mensuration of basal and postprandial C-peptide production over time. Throughout the study, metabolic control was monitored. Fifteen patients were involved in the treatment using WJ-MSCs. At the first month post stem cell therapy the levels of Fasting Plasma Glucose (FPG) started to decrease, meanwhile the levels of Postprandial Plasma Glucose (PPG) reached their lowest by the end of the first year post therapy. At six month of follow-up, the decrease of the mean values of Hb1Ac reached the lowest level. On the other hand, an obvious increase of fasting C-peptide was noticed and the highest peak appeared by the end of the first year post stem cell therapy, and the levels of C-peptide/glucose ratio (CPGR) gradually increased during the full follow-up duration.

MSCs and immune system

Recent studies clearly showed that beside the MSCs ability to differentiate and engage in tissue repair, they have compelling immunomodulatory properties. While the MSCs produce their solvent factors, they can modify the excretion profile of the Dendritic Cells (DCs) creating an expanded production of IL-10, which is an anti-inflammatory cytokine, and a lower production of the factors that can inhibit T cell production [22,23].

These exclusive immunomodulatory functions, made the MSCs approachable for both allogeneic and autologous transplant investigations. For the identical reason, they have been suggested as a treatment for autoimmune diseases, and also for the treatment of empirical models of some autoimmune diseases such as Rheumatoid Arthritis (RA), Systemic Lupus Erythematosus (SLE) [24] and multiple sclerosis (MS) [25-28].

MSCs have shown several immunomodulatory effects after being tested on a variety of animals connected to alloreactive immunity (which is the body's immune reaction to organ and stem cell transplantation), tumor immunity or auto immunity.

One early *in vivo* study showed that systemic infusion of allogeneic MSCs from baboons' bone marrow extended the allogeneic skin's survival up to 11 days in comparison with 7 days in animals not given MSCs [29]. In previous studies, it was presented that the syngeneic host-derived MSCs infusion decreased the rejection rate of allogeneic stem cell grafts in a murine allogeneic bone marrow transplantation model but it was not referred to the possible immunological mechanisms that interacted with these observations.

Conclusion

The aim of our review was to present recent studies on the use of MSCs in the treatment of T1DM. The best results have been obtained by the co-transplantation of MSCs with islet cells, which provided tremendous opportunities for achieving successful long-term functional islet graft survival. There is an increased need to discuss the mechanisms of MSC-mediated cell therapy, and challenges are serious in aspects of engraftment, persistence, tissue targeting, and cell manufacture. Successful management of these challenges and the outcome of clinical trials using MSCs to treat T1DM will decide the future of cell-based therapy for this disease.

Acknowledgments

Special thanks to Miss. Angie Halloum for the Proofreading and linguistic review of the article.

References

1. Corrêa-Giannella ML, Raposo do Amaral AS. Pancreatic islet transplantation. Diabetology & Metabolic Syndrome 2009.1:9.
2. Westenfelder C, Gooch A, Hu Z, Ahlstrom J, Zhang P. Durable Control of Autoimmune Diabetes in Mice Achieved by Intraperitoneal Transplantation of "Neo-Islets," Three-Dimensional Aggregates of Allogeneic Islet and "Mesenchymal Stem Cells". Stem Cells Transl Med. 2017;6(7):1631-43.
3. Ren J, Jin P, Wang E, Liu E, Harlan DM, Li X, et al. Pancreatic islet cell therapy for type I diabetes: understanding the effects of glucose stimulation on islets in order to produce better islets for transplantation. J Transl Med. 2007.5:1.
4. Health Quality Ontario. Pancreas Islet Transplantation for Patients with Type 1 Diabetes Mellitus: A Clinical Evidence Review. Ont Health Technol Assess Ser. 2015;15(16):1-84.
5. Hilling DE, Bouwman E, Terpstra OT, Marang-van de Mheen PJ. Effects of donor-, pancreas-, and isolation-related variables on human islet isolation outcome: a systematic review. Cell Transplant. 2014; 23(8):921-8.
6. Kanak MA, Takita M, Kunnathodi F, Lawrence MC, Levy MF, Naziruddin B. Inflammatory Response in Islet Transplantation. Int J Endocrinol. 2014;2014:451035.
7. Mittal S, Gilbert J, Friend PJ. Donors after circulatory death pancreas transplantation. Curr Opin Organ Transplant. 2017;22(4):372-6.
8. English K. Mesenchymal stem cells to promote islet transplant survival. Curr Opin Organ Transplant. 2016;21(6):568-73.
9. Friedenstein AJ, Petrakova KV, Kurolesova AI, Frolova GP. Heterotopic of bone marrow. Analysis of precursor cells for osteogenic and hematopoietic tissues. Transplantation. 1968;6(2):230-47.
10. Caplan AI. Mesenchymal stem cells. J Orthop Res. 1991;9(5):64-50.
11. Nauta AJ, Westerhuis G, Kruisselbrink AB, Lurvink EG, Willemze R, Fibbe WE. Donor-derived mesenchymal stem cells are immunogenic in an allogeneic host and stimulate donor graft rejection in a nonmyeloablative setting. Blood. 2006;108(6):2114-20.
12. Hematti P, Kim J, Stein AP, Kaufman D. Potential role of mesenchymal stromal cells in pancreatic islet transplantation. Transplant Rev(Orlando). 2013;27(1):21-9.
13. Portmann-Lanz CB, Schoeberlein A, Huber A, Sager R, Malek A, Holzgreve W, et al.

Placental mesenchymal stem cells as potential autologous graft for pre- and perinatal neuroregeneration. Am J Obstet Gynecol. 2006;194(3):664-73.

14. Ezquer M, Arango-Rodriguez M, Giraud-Billoud M, Ezquer F. Mesenchymal Stem Cell Therapy in Type 1 Diabetes Mellitus and Its Main Complications: From Experimental Findings to Clinical Practice. J Stem Cell Res Ther. 2014;4:8.

15. Liu X, Zheng P, Wang X. A preliminary evaluation of efficacy and safety of Wharton's jelly mesenchymal stem cell transplantation in patients with type 2 diabetes mellitus. Stem cell Res Ther. 2014;5(2):57.

16. Xie Z, Hao H, Tong C, Cheng Y, Liu J, Pang Y. Human umbilical cord-derived mesenchymal stem cells elicit macrophages into an anti-inflammatory phenotype to alleviate insulin resistance in type 2 diabetic rats. Stem cells. 2016; 34(3):627-39.

17. Kerby A, Jones ES, Jones PM, King AJ. Co-transplantation of islets with mesenchymal stem cells in microcapsules demonstrates graft outcome can be improved in an isolated-graft model of islet transplantation in mice. Cytotherapy. 2013;15(2):192-200.

18. Dave S. Mesenchymal stem cells derived *in vitro* transdifferentiated insulin-producing cells: A new approach to treat type 1 diabetes. Adv Biomed Res. 2014;3:266.

19. Vanikar AV, Dave SD, Thakkar UG, Trivedi HL. Cotransplantation of adipose tissue-derived insulin-secreting mesenchymal stem cells and hematopoietic stem cells: a novel therapy for insulin-dependent diabetes mellitus. Stem Cells Int. 2010;2010:582382.

20. Carlsson PO, Schwarcz E, Korsgren O, Le Blanc K. Preserved beta-cell function in type 1 diabetes by mesenchymal stromal cells. Diabetes. 2014; 64(2):587-92.

21. Nauta AJ, Fibbe WE. Immunomodulatory properties of mesenchymal stromal cells. Blood. 2007;110(10):3499-506.

22. Abdi R, Fiorina P, Adra CN, Atkinson M, Sayegh MH. Immunomodulation by mesenchymal stem cells: a potential therapeutic strategy for type 1 diabetes. Diabetes. 2008;57(7):1759–67.

23. Van Laar JM, Tyndall A. Adult stem cells in the treatment of autoimmune diseases. Rheumatology. 2006;45(10):1187-93.

24. Augello A, Tasso R, Negrini SM, Cancedda R, Pennesi G. Cell therapy using allogeneic bone marrow mesenchymal stem cells prevents tissue damage in collagen-induced arthritis. Arthritis Rheum. 2007;56(4):1175-86.

25. Deng W, Han Q, Liao L, You S, Deng H, Zhao RC. Effects of allogeneic bone marrow-derived mesenchymal stem cells on T and B lymphocytes from BXSB mice. DNA Cell Biol. 2005;24(7):458-63.

26. Bai L, Lennon DP, Eaton V , Maier K, Caplan AI, Miller SD, et al. Human bone marrow-derived mesenchymal stem cells induce Th2-polarized immune response and promote endogenous repair in animal models of multiple sclerosis. Glia. 2009;57(11):1192-203.

27. Lee RH, Seo MJ, Reger RL, Spees JL, Pulin AA, Olson SD, et al. Multipotent stromal cells from human marrow home to and promote repair of pancreatic islets and renal glomeruli in diabetic NOD/scid mice. Proc Natl Acad Sci USA. 2006;103(46):17438-43.

28. Bartholomew A, Sturgeon C, Siatskas M, Ferrer K, McIntosh K, Patil S, et al. Mesenchymal stem cells suppress lymphocyte proliferation *in vitro* and prolong skin graft survival *in vivo*. Exp Hematol. 2002;30(1):42-8.

29. Nauta AJ, Westerhuis G, Kruisselbrink AB, Lurvink EGA, Willemze R, Fibbe WE. Donor-derived mesenchymal stem cells are immunogenic in an allogeneic host and stimulate donor graft rejection in a nonmyeloablative setting. Blood 2006;108(6):2114-20.