Case Report

Management of Type 1 Diabetes Mellitus with Autologous Mesenchymal Stem Cells

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Abstract

Type 1 diabetes mellitus (DM) is one of the most common chronic metabolic disorders among children. The condition is associated with dysregulation of the immune system resulting in loss of self-tolerance and destruction of pancreatic β-cells by autoreactive T-lymphocytes. Regulation of β-cell homeostasis is vital to maintain optimum blood glucose control as well as prevent the development of complications. Exogenous insulin and oral hypoglycemic agents do not achieve this, as they do not address the core pathology of type 1 DM. This report describes a case of a 17-year-old female patient with fluctuating blood glucose levels and high glycosylated hemoglobin, unresponsive to conventional therapy. After undergoing two sessions of cell-based therapy, within a year, optimum control of blood glucose was achieved along with negative anti-insulin antibodies. The patient was able to discontinue insulin and has not experienced any adverse effects till date. Improvement in general health was noticed, and the patient is now free from any symptoms associated with her former diabetic status. Mesenchymal stem cells (MSCs) possess immunomodulatory and pro-angiogenic properties, which may aid in arresting β-cell destruction. In addition, MSCs may preserve residual β-cell mass and facilitate endogenous β-cell regeneration. These cells are capable of differentiating into glucose-responsive insulin-producing cells, making them ideal candidates in treatment of and prevention of complications in T1DM.

Keywords: *Immunomodulation, mesenchymal stem cells, type 1 diabetes*

Introduction

Type 1 diabetes mellitus (DM) is one of the most common endocrine and metabolic conditions among children. It is an autoimmune disease characterized by islet cell destruction and caused primarily by immune effector cells reacting against endogenous β-cell antigens.[1] Pancreatic β-cell destruction ultimately causes absolute insulin deficiency. Genetic and environmental factors as well as disorder of immune mechanism are thought to be the cause of type 1 diabetes. India has three new cases of Type 1 DM (T1DM)/100,000 children under 14 years of age.[2]

Conventionally, T1DM is treated with insulin therapy, type and dose of which is adjusted based on regular blood glucose monitoring. However, these agents do little in terms of preventing complications such as diabetic ketoacidosis as they do not address the core pathology of the condition.

Cell-based therapy using mesenchymal stem cells (MSCs) has been shown to induce regeneration of pancreatic insulin-secreting cells. These cells also inhibit the immune response against the newly formed β-cells, which, in turn, are able to survive in the altered immunological milieu.[3]

The following case report describes the use of MSCs in T1DM showing dissatisfactory response to conventional therapy.

Case Report

At 12 years of age, the patient first experienced pain in abdomen and increased frequency of micturition. She had multiple fainting spells, which was attributed to general weakness. After repeated episodes of the above symptoms, she was advised to undergo routine investigations to test for diabetes. On noticing irregularities in fasting, postprandial, and random blood glucose levels, the patient was advised to undergo investigations to test for antibodies acting against insulin (C-peptide, islet cell, and glutamic acid decarboxylase). The patient showed positive islet cell antibodies and low C peptide levels (0.2 ng/mL) and was subsequently diagnosed with type 1

How to cite this article: Mahajan PV, Morey A, Subramanian S, Bandre A, Ware H. Management of Type 1 diabetes mellitus with autologous mesenchymal stem cells. CHRISMED J Health Res 2019;6:64-6.

Submission: 12-Feb-18
Revised : 11-Jun-18
Accepted : 12-Jul-18

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Access this article online

Website: www.cjhr.org

DOI: 10.4103/cjhr.cjhr_22_18

Quick Response Code:

DM. Patient was then advised insulin therapy, despite which she continued to have elevated levels of blood glucose, which fluctuated occasionally leading to fainting episodes. She underwent diet modifications and started exercising regularly as advised by her physician but did not achieve much improvement in her general health condition. At the age of 15, she had an episode of diabetic ketoacidosis for which she was hospitalized for a month. Dissatisfied with the results from conventional therapy, she then presented at our hospital with HbA1c level of 11.5.

Consent and ethical approval

Informed consent was obtained from the patient before cell-based therapy as per standard format adopted at our institution. Cell-based therapy protocol was approved by the Ethics Committee at our center.

Stem cell therapy

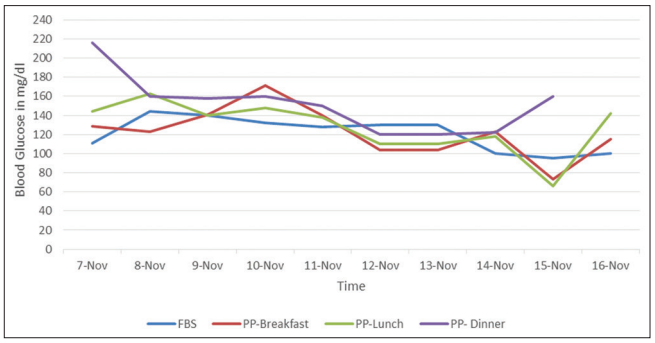
Two sessions of cell-based therapy were planned with an interval of 45 days between the sessions. Approximately 100 mL of bone marrow from the iliac crest and 50–60 mL of adipose tissue from gluteal region was aspirated from the patient's own body (autologous) under local anesthesia. Transplantation of therapeutically effective dose of 500–5000 × 10^6 bone marrow-derived mononuclear cells and 400–1600 × 10^6 adipose-derived stromal vascular fraction was done through intravenous route. The procedure was repeated during each session of treatment. Dose calculation was based on a protocol predesigned at our center with variations depending on the severity of the condition, age, and weight of the patient and presence/absence of comorbid conditions. She was advised to continue moderate intensity exercises and diet as per her existing routine. The patient was also asked to maintain blood glucose chart to observe the changes following each session of therapy.

Results

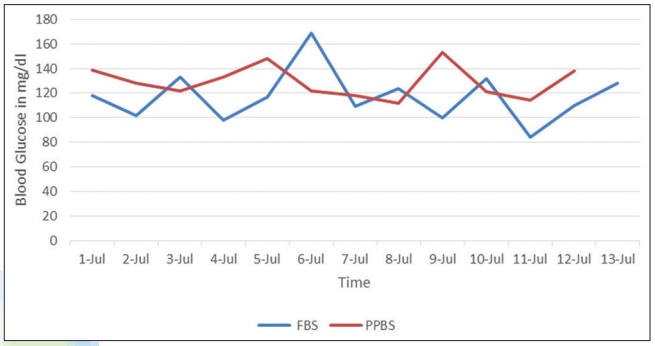
Graphs 1 and 2 depict blood glucose levels following two sessions of cell-based therapy. A month following therapy, patient showed improvement in general health, tolerance to glucose, and an overall reduction in fasting blood sugar. Dose of insulin Lantus was reduced from 10 IU (pretreatment) to 6 IU and she was advised to discontinue insulin NovaRapid. Eight months following MSC therapy, the patient was advised to discontinue insulin Lantus as her blood glucose levels remained stable consistently and her HbA1c level reduced to 7.0. No complaints of increased frequency of micturition or episodes of fainting have been reported till date. Blood investigations done after a year revealed negative islet cell antibody test and raised C peptide levels (1.7 ng/mL). Graph 3 depicts blood glucose levels one year following stem cell treatment.

Discussion

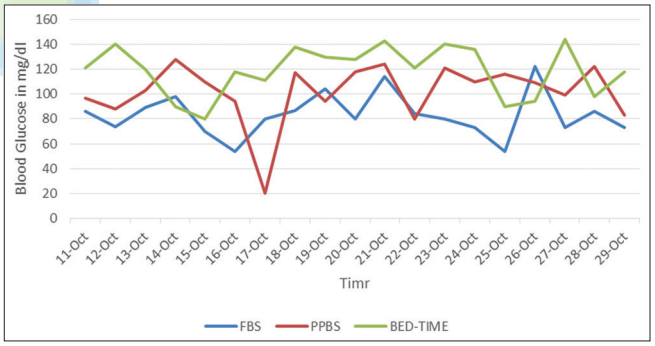
Management of β-cells is an instrumental means to treat T1DM and prevent systemic complications.[4] MSCs are



Graph 1: Blood glucose levels post stem cell therapy session-1 (November 2016). There is a reduction in the blood glucose levels over 10 days after stem cell therapy. (FBS: fasting blood sugar; PP-breakfast: postprandial-breakfast; PP-lunch: postprandial-lunch, PP-dinner: postprandial-dinner)



Graph 2: Six months post stem cell treatment (July 2017). There is an overall control in blood glucose levels 6 months after therapy. (FBS: fasting blood sugar; PPBS: postprandial blood sugar)



Graph 3: Blood glucose levels 1 year after stem cell treatment (October 2017). There is a steady control over blood sugar levels within normal range, 1 year after stem cell therapy. (FBS: fasting blood sugar; PPBS: postprandial blood sugar; Bed-Time: bed-time blood sugar)

capable of self-renewal and have the flexibility to grow into different types of cells. MSCs are capable of differentiating *in vivo* to produce β-cells – the islet cells that manufacture insulin – as well as pancreatic islet cells.[5] Chao *et al*. reported pancreatic islet cell cluster differentiation, which possessed insulin-producing properties, using stem cells derived from umbilical cord Wharton's jelly.[6] Regenerative capacity of the MSCs for islet cell regeneration and reversal of glycosuria for at least 2 months, with an increase in morphologically normal islet cells of pancreas, has also been reported.[7] In this case report, gradual reduction in the

patient's fasting and postprandial blood glucose level has been observed, indicating improved pancreatic function, which can be attributed to islet cell regeneration. This was determined on the basis of negative islet cell antibody test done a year following cell-based therapy.

Clinical trials have evaluated the role of immunomodulation using pharmacological agents and antibodies but have not yielded satisfactory results.[8,9] MSCs have inherent immunomodulatory potential that aids in restoring immune homeostasis in the body.[10] MSCs have also been found to inhibit T-cell-mediated antigen response and correct dysregulation associated with B-cells and natural killer cells.[11] Another crucial feature of MSCs that may be beneficial in T1DM is their ability to selectively migrate to sites of injury through chemokine expression.[12] Anti-inflammatory effects thus exerted play an important role in the maintenance of peripheral tolerance.[13] However, further studies are needed for better understanding of the roles of secreted factors that could determine their fate postdelivery.

Lifestyle modification and diet are known to play a pivotal role in disease control. Moderate-intensity exercise leads to both short- and long-term improvement in insulin sensitivity, thereby leading to reduced blood sugar levels. Physical activity has also been shown to improve lipoprotein profile, cardiovascular health, and prevention of long-term complications arising due to diabetes.[14] It is, therefore, imperative to teach patients to incorporate exercise in their daily lives, in addition to diet management as a means to improve/maintain insulin sensitivity posttreatment. Our patient was following a diet high in fiber, low in saturated fat, and sugars along with optimal protein intake.

Conclusion

Our patient was a known case of autoimmune diabetes. Despite following a strict diet, exercise regimen, and insulin therapy, patient showed poor control over blood glucose levels for many years. Based on our observations, following 1 year after autologous MSC therapy, the patient showed improved control over blood glucose levels as well as improvement in general health while continuing diet and exercise regimen. The patient also showed the gradual reduced requirement of insulin and subsequently could discontinue insulin. We, therefore, speculate that the administration of autologous MSCs has led to the potential regeneration of pancreas with adjunct immunomodulatory effects on anti-islet cell antibodies. Here, our case study sheds light on the use of autologous MSCs as a potential therapy for refractory autoimmune diabetes. Our subsequent work on type 1 diabetes aims to demonstrate the benefits of autologous MSC therapy on a larger cohort with a case–control study design.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that name and initial will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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