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Stem Cells Therapy For Type 1 Diabetes Mellitus

Type 1 diabetes mellitus represents a chronic multifactorial autoimmune disease which leads to the progressive destruction of pancreatic β-cells resulting in the loss of insulin production and secretion[1]. Ultimately with the progression of disease the remaining β-cells will also be destructed resulting in poor glucose control, ketoacidosis, infection, retinopathy with potential loss of vision and many others complications[2]. The existing standard treatment for patients with type 1 diabetes mellitus consists of lifelong exogenous insulin administration which is often associated with debilitating hypoglycemic episodes. Also, it is inconvenient for the patient and does not completely prevent the development of diabetic complications. Another clinical approach is pancreas or islet transplantation. Although it remains the most appropriate option for the treatment of type 1 diabetes mellitus considering the immunopathogenesis of disease, transplantation is restricted by side effects of using of immunosuppressive therapy and an inadequate supply of cadaveric donor tissue[3]. Nevertheless, islet transplantation has paved the way for the use of cellular therapy in the treatment of type 1 diabetes mellitus. The ability of mesenchymal stem cells to differentiate into insulin-producing cells as well as ameliorate immune injury through immunomodulation represents a promising alternative for the treatment of patients with type 1 diabetes mellitus[4].

The first report of treating type I diabetic patients with adipose tissue derived mesenchymal stem cells was published in 2008 by Trivedi H.L. et al. Five patients with type 1 diabetes mellitus were recruited. All of them received infusion of adipose tissue derived mesenchymal stem cells. The follow-up period was 2.9 months. No adverse effects related to the stem cell infusion were recorded in all patients. It was observed that required insulin dosage was reduced up to 50% from the baseline. Moreover, increase of C-peptide serum levels which indicated the endogenous insulin secretion and confirmed recovery and regeneration of islet β-cells was observed in all patients. In addition, it was noticed that patients after stem cells therapy became physically more active and better rehabilitated in their professional and personal lives. Also, in patients with history of diabetic ketoacidosis episodes it was demonstrated that such episodes disappeared in all of them after receiving treatment [5].

In 2009 the results of autologous hematopoietic stem cells using in the treatment of type I diabetic patients were demonstrated in the clinical trial conducted by Couri C.E. et al. Twenty three patients with newly diagnosed type 1 diabetes mellitus had participated in the study. All of them received infusion of autologous hematopoietic stem cells. The follow-up period was from 7 months to 4,8 years. Twenty patients became insulin free after stem cells therapy with good glycemic control. Also, significant increase of C-peptide serum level was noticed in all these patients[6].

In 2010 Vanikar A.V. et al. reported the results of a prospective open-labeled clinical trial in which type I diabetic patients were treated by adipose tissue derived insulinsecreting mesenchymal stem cells. There were eleven patients with type 1 diabetes mellitus who received infusion of mesenchymal stem cells. After the follow-up period which was 23 months in all patients was noticed decrease of HbA1c levels and mean exogenous insulin requirement. Moreover, increase of C-peptide serum levels was observed in all patients. It is important to emphasize that transplantation of mesenchymal stem cells wasn't accompanied by any side effect in all patients[7].

In recent clinical research it was showed that using of autologous adipose tissuederived mesenchymal stem cells in the treatment of patients with type 1 diabetes mellitus can improve islet function and metabolic control in these patients. There were ten patients who received infusion of mesenchymal stem cells. The follow-up period was about 2,5 years. Improvement in mean Hb1Ac, decrease of exogenous insulin requirement, rise of mean serum C-peptide were observed in all patients. Also, glutamic acid decarboxylase antibodies which represents the activity of

the autoimmune process were decreased by 2,7 times in patients after received treatment. Moreover, improvements were maintained during the whole observation period in all patients. In addition, all patients were able to return to their normal lifestyle and normal unrestricted diet. Before the mesenchymal stem cells therapy in six patients there were diabetic ketoacidosis episodes which disappeared in all of them after receiving treatment.

Also, they noticed subjective improvement of their well-being. No untoward effects associated with mesenchymal stem cell therapy were observed[8].

Encouraging results were obtained in a randomized double blind controlled clinical trial conducted by Hu J. et al. in which the long-term effects of the using of mesenchymal stem cells for the treatment of newly-onset type 1 diabetes mellitus were assessed. Twenty-nine patients aged not exceeding 25 years with type 1 diabetes mellitus were enrolled in the study. All of them were randomly divided into two groups. Patients in first group were treated with conventional treatment (insulin therapy) along with intravenous injection of mesenchymal stem cells. The second group was control in which all patients received only conventional treatment. The follow-up period was 21 months. In the first group it was observed progressively reduction of the dosage of insulin per day. Moreover, in 3 patients insulin was discontinued and in 8 patients the daily insulin dosage was reduced by more than 50% of the baseline. In control group the dose of insulin per day increased gradually. In general patients in the first group had a better blood glucose control. Also, a gradual significant decrease of the mean value of HbA1c was noticed in the first group in compare with the control group. In addition there was a progressive increase of mean fasting C-peptide levels in the first group. While in the control group, the mean C-peptide levels decreased gradually. During the follow-up period ketoacidosis appeared in three patients in the control group while in the first group no ketoacidosis was observed. It is important to notice that there were no adverse reactions after stem cell therapy in any of the patients[9].

In 2013 two case reports were published by Dave S.D. et al. in which therapy by adipose tissue-derived mesenchymal stem cells along with bone marrow-derived haematopoietic stem cells was used in two men with type 1 diabetes mellitus aged 22 and 15 years respectively. They were treated by infusion of stem cells according to receiving of exogenous insulin therapy. The follow-up period was two years for the first patient and one year for the second. Over the observational period they had stable blood sugar levels with good glycemic control. The daily insulin dosage was reduced significantly. Moreover, both of them became free of diabetic ketoacidosis episodes after stem cells treatment [10].

One year later Dave S.D. et al. published one more clinical case in which therapy by autologous adipose tissue-derived mesenchymal stem cells along with bone marrowderived haematopoietic stem cells was used in a 9-year-old boy with insulin-dependent diabetes mellitus. Over 2 years of follow up period the patient had stable blood sugar levels with good glycemic control (glycosylated haemoglobin was 6.4%)[11].

It is important to emphasize that at the clinical onset of type 1 diabetes mellitus in most patients there are only 20-30% of their original β-cell are remained. Moreover, with the progression of disease these preserved β-cells will also be destroyed. This leads to poor glucose control, ketoacidosis and development of serious diabetic complications such as retinopathy with potential loss of vision, nephropathy resulting in renal failure, sexual dysfunction and many others[12]. Therefore, stem cells therapy should be started in patients with type 1 diabetes mellitus as soon as possible for saving a larger number of residual functioning β-cells[13].

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