# The Effect of Fetal Liver-Derived Cell Suspension Allotransplantation on Patients with Diabetes: First Year of Follow-up

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***Received: 20 May 2012; Received in revised form: 27 Jun. 2012; Accepted: 19 Jul. 2012***

**Abstract-** Stem cell-based therapies have recently opened up new horizons for treatment of various types of diseases including diabetes mellitus. However, long-term efficacy and safety of these novel modalities still remain a serious question. Hereby, we aim to report the one-year follow-up results in the diabetic patients who underwent fetal liver-derived hematopoietic stem cell allotransplantation. Fifty six patients with type one (n=30) and type two (n=26) diabetes, aged 10-58 years old (32.8 ± 16.3) were divided into the intervention and placebo group. The patients in the intervention group underwent fetal liver-derived hematopoietic stem cell transplantation while the patients in the placebo group received 5 ml of normal saline both via an intravenous route. The patients were visited at regular intervals to evaluate the efficacy of transplantation in glycemic control as well as possible complications. In the 6$^{th}$ month of the follow-up, there was a significant decrease in $HbA_1c$ levels in all groups without any rise in the fasting c-peptide. However, none of the precipitants transiently or continuously became insulin free in the first year after transplantation. It can be concluded that, in this study, fetal liver-derived hematopoietic stem cell transplantation had no significant effects on glycemic control. The heterogeneity of our patients might account for the negative results. Hence, longer follow-up results will be reported in the near future.



*Acta Medica Iranica*, 2012; 50(8): 541-546.

**Keywords:** Diabetes mellitus; Fetal hematopoietic stem cells; Cell therapy

## Introduction

Around 5% of people in developed countries suffer from one of the eighty classified autoimmune diseases (1). Type 1 diabetes is characterized by autoimmune destruction of β-cells in the pancreatic islets (2). By presenting islet autoantibody, most people will progress to diabetes in 5-10 years. As the autoimmunity develops, function of β-cells dwindles, so does the possibility of performing a successful interventional immunomodulation (3). In type 2 diabetes, the β-cell loss mostly happens via apoptosis but immunological mechanism also plays a role (4-8). In a cluster of patients with type 2 diabetes named " latent autoimmune diabetes in adults (LADA)" autoantibodies to islet cell cytoplasm (ICA) and glutamic acid decarboxylase (GAD) were detected (2,9).

In 1981, researchers for the first time isolated stem cells which are undifferentiated cells with a great ability for proliferation, differentiation to other types of cells and self renewal. Since then, using stem cells for treatment of various diseases has opened up new horizons for endocrinologists (10,11). Results of many studies in the last decade indicate that producing of insulin secreting cells from pluripotent stem cells is possible both *in vitro* and *in vivo* (12-16).

Several studies supported the effect of hematopoietic stem cells (HSCs) on reset/modulation of immune system (17). Such studies indicate a promising treatment role for cell therapy in autoimmune diseases such as type 1 diabetes (17,18).

Many sources have been recognized for HSCs research and therapy and can be classified as adult, embryonic and fetal HSCs. In the first clinical study which investigated the effect of autologous hematopoietic stem cells (adult HSCs) transplantation in newly diagnosed type 1 diabetes, patients received high doses of immunosuppressive agents before the stem cell

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transplantation. The study showed considerable results on inducing complete remission (insulin independence) in most of the patients (19,20). Furthermore, it has been shown that direct injection of autologous bone marrow-derived stem cells into the pancreas of patients with type 2 diabetes leads to significant increase of endogenous insulin secretion (21). Fetal HSCs has some advantages over their adult counterparts including higher homing and engraftment potency, greater multipotential properties, lower immunogenicity and greater differentiation potency for transplantation (22). Although development potential of fetal HSCs is lower than pluripotent embryonic stem cells, they have the ability to differentiate into almost all cell types (22,23). Furthermore, there are serious concerns about possibility of tumorigenicity in transplantation of embryonic derived stem cells (23,24). Therefore, human fetal tissue such as fetal liver is a promising source of HSCs which have high self-renewal capacity and low immunogenicity.

Regarding the ability of stem cells to differentiate into insulin producing cells (25-27), besides their immunomodulatory function (28-30), this double-blind placebo controlled clinical study aimed to investigate the effect of fetal liver-derived cell suspension allotransplantation on patients with diabetes without proceeding immunosuppressiveagents.

## Materials and Methods

The study protocol was approved by the ethics committee of Endocrinology and Metabolism Research Center (EMRC) of Tehran University of Medical Sciences (ethical code number: E-0089) (31-33). An informed consent was obtained from each patient or his/her parents before their enrollment in the study. The study began in 2006. Hereby, we are describing the results of the first year follow-up after the transplantation.

### Patients selection

Thirty patients with type 1 diabetes and twenty-six with type 2 diabetes were selected according to the on following criteria: Age range between 10-60 years old, duration of the disease up to 20 years, blood glucose under 15mmol/l (270 mg/dl).

### Exclusion criteria

Acute vascular inflammation, acute thrombosis, recent retinal hemorrhage, pulmonary hypertension, cor pulmonale, bone marrow malignancy, end stage diseases, infections, and signs of refractory complications.

### Randomization

Patients were allocated to receive either fetal liver-derived cell suspension (34) from human legally aborted early fetus (35) aged 6 -12 weeks (intervention group) or placebo solution (placebo group) by permuted balanced block randomization method.

### Assessments

All volunteer patients with diabetes who were matched with inclusion/exclusion criteria were checked for viral infections including HCV, HBV, HIV, and urogenital infections before the final enrollment.

To undergo transplantation, all patients were admitted to the hospital. On the day of hospitalization, primary clinical examination and laboratory data (including FBS, $HbA_1c$, fasting serum c-peptide, CBC, liver function tests, lipid profile tests and U/A) were collected. This data was recollected in the next follow-up visits in the $1^{st}$, $4^{th,}$ $12^{th}$, $24^{th}$ and $56^{th}$ weeks after the cells infusion. Each follow-up visit included a complete physical examination and laboratory tests. In order to optimize diabetes care, each precipitant had access to a special 24-hour phone line physician during the first year of the follow up.

### Stem cell preparation

Fetal liver-derived hematopoietic stem cells (HSCs) were isolated from legally and aborted human fetuses aged 6–12 weeks after obtaining an informed consent from the parents (mother or both of the parents) (33). In order to determine chromosomal abnormalities and to identify the sex of the donated fetus, karyotyping was done for each fetal sample.

Whole fetal liver was placed in Hank's balanced salt solution without calcium and magnesium (HBSS, Sigma, USA) and dissociated and homogenized mechanically. The cell suspension was filtered through nylon mesh to undergo transplantation; and then, isolated cells were cryopreserved using 5% dimethyl sulfoxide (DMSO) in HBSS, (Wak Chemie, Germany) with a programmable freezer, and were transferred to liquid nitrogen for long term storage. Before transplantation, samples were thawed at $37^{o}C$ and cryoprotectant was diluted by 5 milliliter normal saline before infusion. Total cell count in the prepared suspension was approximately $35\text{-}55\times10^{6}$, twenty percent of which was recognized as hematopoietic ($CD34^{+}$) stem cells (34).

The suspension was checked before, during, and after processing for aerobic, anaerobic and fungal contamination as well as viral infections. Rubella, Herpes Simplex Virus, Cytomegalovirus, Chlamydia, Mycoplasma Homonis, Toxoplasma Gondii and Treponema Pallidume were checked using ELISA (enzyme linked immunoassay). DNA/RNA extraction and polymerase chain reaction (real-time PCR) were done for checking viral contamination (HBV, HCV, and HIV). After evaluating the results, cell samples were known qualified for the transplantation (34) .

**Placebo solution**

Injectable normal saline at the dosage of 5 ml was considered as the placebo solution.

**Intervention**

On the day of transplantation each participant in the intervention group received fetal liver-derived cell suspension at the dosage of approximately $35\text{-}55\times10^6$ cells ($7\text{-}11\times10^6$ $CD34^+$ HSCs) in 5 milliliter of normal saline intravenously. Participants in placebo group received 5 milliliter of normal saline intravenously.

**Data analysis**

In order to analyze the collected data, t-test was performed comparing the continuous variables between intervention and placebo group with a normal distribution. As c-peptide did not have a normal distribution, we used the non-parametric test (Mann-Whitney) and considered the median as the central measure. All statistical tests were carried out by SPSS software (version: 17.0) and significance level was set at 0.05.

## Results

Fifty six patients with type 1 (n=30) and type 2 (n=26) diabetes mellitus aged 10- 58 years old (mean ± SD; 32.8 ± 16.3) were recruited to the study. The patients had been diagnosed as diabetics for 0.5- 11 years (mean: 5.0, SD: ± 2.8). There were no significant differences in demographic variables and baseline data between intervention and placebo groups. The selected patients mostly did not have a history of diabetic ketoacidosis (DKA) (n=51). When the patients were divided into two groups according to their type of diabetes, no significant differences in demographic variables were observed between type 1 and type 2 diabetic patients (Table 1).

No acute adverse effects such as fever and other allergic reactions were seen on the day of transplantation as in later months. None of the patients became insulin free over the first year after transplantation.

Table 2 compares the biochemical factors between two groups regarding the type of diabetes in the $6^{th}$ and $12^{th}$ months of follow-up.

In both type one and type two diabetes groups, the level of serum c-peptide did not change significantly within the groups or between them.

In type 1 diabetes group, by the $6^{th}$ month of follow up $HbA_1c$ significantly decreased compared to baseline but there were no significant differences in the level of $HbA_1c$ between placebo and intervention group ($P$=0.917). In type two diabetes group, by the $6^{th}$ month of follow-up, $HbA_1c$ significantly decreased within both placebo and intervention groups but $HbA_1c$ was significantly lower in placebo group compared to the intervention group ($P$=0.046). No other significant differences were seen in other variables between two groups or within groups (Table 2).

**Table 1.** Demographic data of enrolled patients.

| Type of diabetes | Variable | Cell therapy group | Placebo group | *P*-value |
|---|---|---|---|---|
| Type 1 | Age (mean ± SD) (year) | 21.61 ± 10.53 | 21.35 ± 9.80 | 0.731 |
| | Female % (n) | 46.2 (6) | 52.9 (9) | 0.713 |
| | Duration of diabetes(mean ± SD) (year) | 4.23 ± 2.21 | 4.11 ± 2.86 | 0.198 |
| Type 2 | Age (mean ± SD) (year) | 48.33 ± 9.75 | 42.81 ± 13.63 | 0.213 |
| | Female % (n) | 80.0% (12) | 63.6 (7) | 0.353 |
| | Duration of diabetes (mean ± SD) (year) | 6.03 ± 2.55 | 6.04 ± 3.27 | 0.150 |

**Table 2.** FBS , HbA1c and c-peptide levels in the patients based on type of diabetes in 6th and 12th month of follow-up.

| Type of diabetes | Factors | Base line | | | 6mobth | | | 1 year | | | Repeated ANOVA | | Group* time |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Cell therapy | placebo | *P* | Cell therapy | placebo | *P* | Cell therapy | placebo | *P* | Cell therapy | placebo | *P* |
| Type 1 | FBS | 219.0 ± 126.4 | 223.2 ± 125.1 | 0.927 | 239.8 ± 129.2 | 224.7 ± 0.99 | 0.720 | 187.1 ± 122.5 | 173.4 ± 91.9 | 0.739 | 0.418 | 0.283 | 0.95 |
| | HbA1c | 10.8±2.0 | 10.1±1.4 | 0.342 | 8.3±1.1 | 8.3±1.6 | 0.917 | 9.2±1.6 | 9.3±1.8 | 0.884 | <0.001* | <0.002* | 0.66 |
| | c-peptide (median) | 0.28 ± 0.60 (0.05) | 0.27 ± 0.49 (0.12) | 0.96 | 0.26 ± 0.52 (0.07) | 0.32 ± 0.75 (0.03) | 0.80 | 0.32 ± 0.75 (0.05) | 0.30 ± 0.80 (0.05) | 0.89 | 0.57 | 0.49 | 0.42 |
| Type 2 | FBS | 166.0 ± 56.6 | 151.8 ± 69.6 | 0.570 | 168 ± 73.3 | 129.3 ± 32.4 | 0.110 | 184 ± 86.0 | 134.6 ± 27.2 | 0.112 | 0.573 | 0.345 | 0.30 |
| | HbA1c | 9.4 ± 1.6 | 9.2 ± 1.2 | 0.659 | 7.9±1.3 | 7.0 ± 0.86 | 0.046* | 8.3 ± 2.0 | 7.4 ± 2.2 | 0.396 | 0.003* | 0.002* | 0.33 |
| | c-peptide (median) | 2.2 ± 0.9 (2.4) | 2.2 ± 0.9 (2.1) | 0.91 | 2.1 ± 1.0 (2.3) | 1.9 ± 1.3 (2.1) | 0.50 | 2.5 ± 1.2 (2.9) | 2.1 ± 1.6 (2.0) | 0.55 | 0.48 | 0.17 | 0.63 |

## Discussion

Over the past few years, there have been considerable advances in the field of stem cell biology. Stem cells have been recognized to have a great potential to give rise to cells of various cell lineages. Some reports suggest that hematopoietic stem cell transplantation holds a great potential for treatment of autoimmune diseases such as autoimmune diabetes mellitus (10,11,28, 36). In this study, 56 patients with diabetes (type 1 =30 and type 2= 26) aged 10-60 years old were enrolled in the study (Table 1).

Significant decrease in $HbA_1c$ levels in the 6th month of follow-up without increase in the level of c-peptide, mostly contributes to tight or better control of blood glucose (Table 2). Even though the selected participants of our study were matched regarding demographic data, wide range of both age (ranged between 10 to 58 years old) and duration of diabetes (ranged between 6 months to 11 years) could be responsible for the negative results in our study (37).

Although in an investigation by Voltarelli *et al*., insulin independence was seen in most patients after autologous HSCs transplantation which was proceeded by non-myeloablative regimen, utilizing the non-myeloablative regimen lead to some adverse side effects in the patients (19). Voltarelli *et al.* contributed their great results to the synergistic effect of both immunomodulatory and differentiation capacities of stem cells with non-myeloablative regimen (19,20,38). Moreover, it seems that tight inclusion criteria of Voltarelli *et al*. especially diabetes duration of less than 6 weeks (without the history of DKA) as well as more potential benefits from immunomodulation intervention, had importan roles in obtaining such considerable results (29).

Investigation of Bhansali *et al.* on efficacy of autologous bone marrow-derived stem cell transplantation in patients with type 2 diabetes resulted in considerable reduction in insulin doses which was correlated with stimulated c-peptide response at the baseline (21). In their study, the participants were precisely matched as following: Negative results for GAD antibody test (anti-GAD), duration of type 2 diabetes for at least 5 years, failure of triple oral anti-diabetic agents, receiving high doses of insulin (≥0.7 U/kg/day) for at least 1 year as well as the same dose of oral anti-diabetic agents for at least 3 months before enrollment (21). Compared with the inclusion criteria in Bhansali *et al*. study, we assume that the heterogeneity of our patients is the reason for our negative results in type 2 diabetes groups. The fact that our patients were either on insulin or triple oral anti-diabetic drugs and had no history of having stable drug dosages before the study, make it impossible to run an authentic assessment analysis.

In designing this study, both differentiation and immunomodulatory capacities of stem cells had been assumed, with an emphasis on the later one (21,25,26,28-39) .Considering that HSCs are capable of

the modulating immune system as well as transforming into other cells such as β-cells, it would be more reasonable if only patients with newly diagnosed type 1 diabetes with measured serum anti-GAD were enrolled in this study. In addition, area under the curve of c-peptide should be measured instead of fasting serum c-peptide. The last but not the least, more limited ranges of diabetes duration should be considered so that it would be possible to perform comparing statistical study on eventual changes in the necessary daily insulin dosage of patients before and after the cell infusion in follow-up sessions.

Although our investigation method is unique, we have not yet tried to publish the results of this study over the past 3 years due to the defects in the design of the protocol. Hence, the pitfalls had been taken into consideration and had set more precise inclusion criteria in our next study. With respect to the safety issues of stem cells in treatment of various diseases including diabetes (40,41), follow-up visit of the patients in this study still continues and the results will be reported in the near future.

## Acknowledgment

We would like to express our sincere gratitude and appreciation to the following, without whom this project would not be possible: Irina Votyakova for cell suspension preparations and processing, Dr. Ensieh Nasli-Esfahani and Dr. Reza Heidarpour for performing diabetes care of the patients on the day of hospitalization and Ms Samimeh Shahbazi for her outstanding work as a nurse.

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