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Editorial

Application of Fetal Stem Cells in Diabetes: Iran's Experience

Ali TOOTEE, Ensieh NASLI ESFAHANI, *Bagher LARIJANI

Diabetes Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran

***Corresponding Author:** Email: emrc@tumc.ac.ir

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Diabetes mellitus is a chronic and disabling disease, which imposes a substantial burden on public health in both developing and developed countries. Patients suffering from diabetes mellitus are at higher risk of being affected by different complications related to cardiovascular, renal, ophthalmic, neurological, cerebrovascular, and peripheral vascular systems (1). Moreover, mortality rate of diabetes is considerably high and it is reported that worldwide, 3% of deaths can be attributed to diabetes (2).Currently, based on the reports of the WHO, more than 220 million people suffer from diabetes in the world (3). In the Middle East, recent reports from different countries in the region indicate that the prevalence of both type 1 and type 2 diabetes are alarmingly increasing (4, 5).

To date, available treatment options for diabetes, which include oral antidiabetic agents and insulin therapy, do not fully prevent from diabetes-related complications (6, 7). However, it is demonstrated that preservation or restoration of pancreatic beta cell's function, even to small extents, may significantly prevent from short-term and long-term complications of diabetes (8-13). Moreover, side effects of antidiabetic agents are intolerable for some patients and insulin therapy is cumbersome. Besides, it is difficult to maintain blood sugar levels within the normal range with the use of currently available conventional diabetes treatment strategies. Therefore, it is imperative to develop new strategies for treatment of diabetes with the objective of preservation or restoration of insulin-secreting beta cells.

Hitherto, several potentially curative approaches are developed for treatment of diabetes. One such approach is immunosuppression by means of either immunosuppressive drugs or monoclonal antibodies. However, complete cure has remained elusive and adverse effects far outweighed benefits (8, 14-18). Although limited by shortage of donors and defects in the currently available immune suppression methods, whole pancreas transplantation is considered as another curative option for treatment of diabetes with quite acceptable safety and effectiveness (19, 20). Pancreatic islet cell transplantation is yet another promising curative option for diabetes with a favorable future although the procedure is hindered by shortage of donors and its progress is dependent on discovery of new methods to induce immune tolerance to the donor beta cells (21). In Iran, Endocrinology and Metabolism Research Institute of Tehran University of Medical sciences has attained remarkable achievements in this field and has even established a pancreatic islet transplantation facility for islet isolation with the first successful isolation performed in 2010 (22).

Stem cells, believed to have the potential to be used as an alternative to pancreatic islet cells, are undifferentiated cells, which are capable of proliferation, regeneration, and conversion to differentiated cells (23). They can be harvested from two different sources on which base they are

broadly categorized into two different categories: adult and embryonic stem-cells.

Since 1980s when the science of stem-cell research evolved significantly, many different diseases have been cured with the use of autologous transplantation of adult stem-cells and the technique is now used more often than allotransplantation considering its low immunogenicity and minimum requirement for immunosuppression (24). Autologous transplantation of adult stem-cells has already been used for treatment of type 1 DM with considerable improvement in daily insulin dose and c-peptide levels (25-27). In one study carried out by our institute in 2010, autologous transplantation of mesenchymal stem cells, which were obtained through bone marrow aspiration and injected in two sessions, demonstrated significant decrease in the required insulin dose in a few patients with type-1 diabetes (28). The results of our study, which were presented as a poster presentation at the Endocrine Society's 95th Annual Meeting and Expo (Endo 2013) in San Francisco, demonstrated no side effects and the observed reduction in total daily insulin dose in a few patients was significant. In a different study, in type 2 diabetes too, injection of autologous bone marrow stem-cells (without separation into HSC or MSCs) directly into the pancreas of diabetic patients demonstrated a significant reduction in insulin requirements (29). However, considering the fact that diabetes has a genetic etiology in many cases, there seems the possibility that the defective gene is transferred to the cultured cells and returned to the patients' body in autologous transplantation procedure, resulting in nesting of defective beta cells.

Since the advent of HLA typing in 1960, allogeneic transplantation of adult stem-cells has been widely used for treatment of different diseases (24). However, in allograft transplantation, similar to autologous transplantation, as the donor needs to be a first-degree relative of the patient in order to minimize the risk of rejection of the graft, there is the risk that the relative also carries the defective genes, and consequently, again, damaged beta-cells can be transplanted without any significant therapeutic achievement. Moreover, in allograft transplantation there is the need for immune-suppression, which poses its own side effects. Therefore, ideally, cells with maximum differentiation potential and lowest immunogenicity are required for provision of a renewable source of insulin-secreting pancreatic beta cells.

Embryonic stem-cells have the highest potential for differentiation into insulin-secreting pancreatic beta-cells (30) and their application does not necessitate immunosuppressive treatment (31). Although previous studies suggested that embryonic stem-cells lack many functional specifications of bona fide β cells, recent findings have demonstrated that there exists the possibility of generation of hundreds of millions of glucose-responsive β cells from embryonic stem-cells (32). The derivation of mouse embryonic stem cells was first reported in 1981 followed by derivation of human embryonic stem cells in 1998 (33). Since then, this therapeutic method has opened new horizons for treatment of different diseases including both type 1 (34) and resistant type 2 (25) diabetes as a novel curative option. However, the use of embryonic stem cells was later hindered by the risk of tumogenicity many believed it would pose (35), ethical concerns, and in many countries, restrictive legislations (36).

Fetal stem cells can be obtained from different fetal tissues, including blood, bone marrow, liver and kidney. In the recent years, findings of different clinical trials have demonstrated that a wide range of diseases from autism (34) to diabetes (37) have been treated with the using fetal stem-cells with significant success. At the EMRI we have attained considerable achievements the field of clinical isolation and purification of fetal hematopoietic stem cells for treatment of diabetes mellitus (38). Both fetal HSC and MSC, which can be obtained from several fetal tissues in the first trimester of gestation, have been demonstrated to be advantageous over their adult counterpart because of their better intrinsic homing and engraftment, greater multipotentiality and lower immunogenicity. Moreover, ethical concern over the use of fetal stem cells is less intense in comparison with embryonic stem cells and they show greater differentiation potential in comparison with adult stem

cells (39). Besides, contrary to adult stem-cells, there is no need to culture the cells when fetal stem-cells are used. At the EMRI, we have successfully isolated and purified fetal hematopoietic stem cells, which can be used for treatment of diabetes mellitus.

We have carried out a number of clinical trials using liver-derived fetal stem-cells for treatment of diabetes (31) at the Endocrinology and Metabolism Research Institute of Tehran University of Medical Sciences. Our first experience demonstrated no significant decrease in the dose of insulin needed for treatment of the patients, a finding that can be attributed to the heterogeneity of the patients and defective inclusion criteria (31). In our next experience with tighter inclusion criteria in which only clinically diagnosed type 1 diabetic patients were included(the results are to be published shortly), we observed significant insulin-free periods (from 4 to 24 months) in a few patients (40).

In contrast to the risk of tumogenicity embryonic stem cells pose, the use of fetal stem-cells is demonstrated to be comparatively safe, and apart from a few cases of benign tumor formation following the procedure (41-43), including one case of meningioma in one of our studies (44) (the details to be published shortly), to our knowledge, no tumogenicity has been associated with it hitherto. The safety of the application of fetal stem-cell therapy is the subject of another paper we are to publish shortly (45). However, as fetal stem-cell therapy is quite a novel technique, its safety is not yet fully well elucidated and there remain concerns about it.

Although our findings can be considered as groundbreaking in the field of curative treatments for diabetes, more clinical trials with tighter inclusion criteria are warranted to better demonstrate the effectiveness of fetal stem-cell therapy and its superiority over the usage of mesenchymal stem-cells (40).

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