



Therapeutic Uses of Stem Cells in Endocrinology- Review Article

Ensieh NASLI ESFAHANI¹, Ardeshir GHAVAMZADEH², *Bagher LARIJANI³

1. *Diabetes Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran*
2. *Hematology-Oncology and Stem Cell Transplantation Research Center, Tehran University of Medical Sciences, Tehran, Iran*
3. *Endocrinology and Metabolism Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran*

***Corresponding Author:** Email: Larijanib@tums.ac.ir

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Abstract

Background: Because of the ability of proliferation, regeneration, conversion to differentiated cells and tissue producing, stem cell therapy has important clinical implications for treatment of different diseases. In this chapter we discuss different kinds of stem cells that have been used in treatment of neurologic diseases, gastrointestinal diseases, heart diseases, bone disease, kidney disease, chronic wounds, graft versus heart disease, sepsis and respiratory diseases. Then we will discuss stem cell therapy in treatment of diabetes which is one of the most important diseases of Endocrinology and after that we will provide a brief summary of ethical challenges of stem cell transplantation.

Keywords: Stem-cell therapy, Endocrinology, Diabetes

Introduction

What are stem cells?

Stem cells are non-differentiated cells that have the ability of proliferation, regeneration, conversion to differentiated cells and tissue producing. Regeneration means that these cells have the ability of asymmetric division which one of the resulting cells remains as stem cell and another cell, which is called daughter cell, becomes one cell of germ layer. Stem cells may remain without activity for long times, after that they can enter cell division again (1, 2).

For the first time in 1981, researchers could isolate stem cells from mouse embryos. More accurate studies on the biology of mouse stem cells led to discovery of methods for separation of stem cells from the human embryo in 1998 (3-5).

Stem cells are divided into two groups: embryonic and adult stem cells. Embryonic stem cells are derived from zygote cell which is fertilized in vitro and usually is 4-5 day embryo which is in form of a hollow ball called blastocyst. Blastocyst is composed of three parts: the trophoblast layer that is surrounding blastocyst, a hollow cavity inside the blastocyst, and inner cell mass that changes to embryo.

Since zygote cells can differentiate into placenta and fetal cells, sometimes they are considered as the only true totipotent stem cells. Because the inner cell mass of the blastocyst does not have the ability to differentiate in to placenta cells, it is called the pluripotent cell.

Non-differentiated cells other than embryonic stem cells can be found in differentiated cells of specific tissues after birth. These cells are called as adult or non-embryonic stem cells but the better word for them is "somatic stem cells" because they also exist in children and umbilical cord. These cells divide into two main categories: hematopoietic stem cells that can differentiate into blood cells and mesenchymal stem cells that are less differentiated. Nose, muscle, liver, skin, brain, retina and limbus of the eye are the other sources of adult tissue. Important advantage of adult stem cells over embryonic stem cells is because of the

fact that they can be obtained without the need for destruction of embryo (6, 7).

Different types of stem cells can be seen in Table 1. The pluripotent stem cell differentiates into the multipotent cell of 3 different germ layers (ectoderm, mesoderm and endoderm layer). The multipotent cell differentiates into unipotent cell of a specific cell lineage within its germ layer (8).

If differentiation process is successful, the resulting cell will be called as progenitor cell or stem cell-like cells that have the ability of regeneration (6).

Table1: Different categories of stem cells

Cell type	Definition
Totipotent cell	Ability of differentiation into all cell types
Pluripotent cell	Ability of differentiation into cells which are placed in fetal layers
Multipotent cell	Ability Of differentiation into cells of specific categories (in fetal layers)
Unipotent cell	Ability Of differentiation into only one type of cell (different from non-Stem Cell because of the ability of regeneration)

Stem cell therapy in different diseases

Stem cells have been studied in treatment of various diseases. In this chapter we aim to evaluate cell therapy in treatment of neurologic diseases, gastrointestinal diseases, heart diseases, bone disease, kidney disease, chronic wounds, graft versus heart disease, sepsis and respiratory diseases. Then we will discuss stem cell therapy in treatment of diabetes and after that we provide brief summary of ethical challenges of stem cell transplantation.

Neurologic disease

Parkinson is a disease that is characterized by progressive destruction of dopaminergic neurons in substantianigra of midbrain. Motor Signs such as bradykinesia, stiffness and rest tremor are due to destruction of terminal dopaminergic neurons in basal ganglia including caudate and putamen which results in balance disorders (9).

Levodopa can improve the symptoms, but it cannot prevent neurons from destruction. Today cell therapy is considered as a novel treatment and different types of cells have been studied for these patients such as Embryonic stem cells (10), Mes-

enchymal cell (11), induced pluripotent stem cells (12), Fetal neural stem cells (13), Stem cells derived from adult brain (14), Mature multi potent stem cells (15). Significant functional and behavioral improvement was reported.

Amyotrophic Lateral Sclerosis

(ALS) is a fatal neurodegenerative disease that is characterized by progressive destruction of neurons of spinal cord and motor neurons of cortical brain (16). ALS is a progressive disease that impairs movement of the diaphragm and results in death. Replacement of human neural stem cells, astrocytes replacement, Hematopoietic stem cells and mesenchymal stem cells has been used for treating this disease in various studies. Some of the studies have reported that stem cell therapy could cause protective effects for motor neurons and improve symptoms.

Alzheimer is a progressive, irreversible neurodegenerative disease that is the most common form of dementia among older people. Hereditary mutations and numerous genetical, environmental and acquired risk factors that none of them is curable have been proposed as the causes of this dis-

ease. Neural stem cells, Neural precursor cells derived from embryonic stem cells and mesenchymal stem cells are used in Alzheimer cell therapy. These cells caused significant improvement in behavioral disorder and memory and there was no sign of tumor (17-19).

Stroke causes loss of large number of neurons and glial cells. Cell therapy opens up new horizons in the treatment of this disease through facilitation of neurons regeneration process. Animal studies and several preclinical trials confirm effect of cell therapy on functional improvement after stroke. Although the mechanism of these cells is still unknown, integration to host brain cells, protection of neurons, regulation of immune system, increase of internal healing processes, vascular regeneration, stimulation of host brain plasticity and use of internal progenitors are its possible causes. Different types of cells that have been used for this purpose are Neural progenitor cells derived from human Embryonic stem cells (20), Neural progenitor cells derived from embryos (21), Immortalized cell lines (22), stromal cells of human adipose tissue (23), Peripheral blood cells (24), Blood cells of human umbilical cord (25), mesenchymal cells (26), Bone marrow stromal cells (27).

Spinal cord injury is one of the severe neurological damages that cause loss of nerve tissue and subsequently loss of sensory and motor function. There is no treatment for regeneration of this damage. This damage may be repaired via replacement of stem or progenitor cells (8). Embryonic stem cells (28), Neural stem cells (29), olfactory cells (30), mesenchymal cells (31), Progenitor Stem Cells (32) have been studied in animal models and phase I/II clinical trial (mesenchymal stem cell), and some of them reported positive results in increase of remyelination and improvement of motor activity. According to the results the best time for use of these cells is the acute and subacute phase of injury (31).

Multiple Sclerosis (MS) is a chronic inflammatory and degenerative disease in central nervous system that is probably associated with autoimmunity of CD4 T-cells (33). Immunomodulator drugs are current treatment of MS, but long term effect of these drugs is so limited that only 30 percent of

patients in long-term benefit from these drugs (34, 35). Embryonic stem Cells (36), Adult neural stem cells (37) and mesenchymal stem cells (38) have been used for MS.

Duchenne muscular dystrophy is a recessive X-linked disease in which reduction of dystrophin presentation in sarcolemma of muscle fibers causes progressive muscle weakness (39, 40). After examining different types of stem cells such as Myogenic progenitor cells (41), Satellite cells (42), Bone marrow stem cells (43), mesoangioblasts (44), pericytes (45) and CD 133+ derived from blood or muscle (46, 47) it was shown that some of these stem cells have the ability of differentiation to muscle fiber and can be used in Duchenne patients.

Gastrointestinal diseases

Inflammatory bowel disease, Crohn and ulcerative colitis have been named as inflammatory bowel diseases. The exact cause of these diseases is still unknown, but immune system dysfunction is one of their causes. Since stem cells are immunoregulator, also because of the ability of transdifferentiation and cell fusion it seems that they have a positive effect in improvement of these diseases (48). Radiation-induced intestinal damage Radiotherapy after pelvic or abdominal tumors may cause intestinal mucosal damage, loss of villi, mucosal atrophy and intestinal dysfunction (49, 50). Previous studies have shown that stem cells derived from bone marrow can differentiate into various mesenchymal tissues such as intestinal cells, but low replacement rate of these cells in intestinal mucus has limited the practical use of stem cells derived from bone marrow in radiation-induced enteropathy (51-54).

Liver diseases, nowadays stem cell transplantation have been suggested as a novel method in treatment of cirrhosis. In laboratory studies, different types of stem cells were used for this purpose such as embryonic stem cells, mesenchymal stem cells, annex stem cells and progenitor endothelial cells. Also laboratory studies have shown that primary hepatocytes can be replaced in liver, spleen, peritoneal cavity and other sites outside the liver (55-59). A number of human studies about the use

of autologous mesenchymal stem cells in cirrhotic patients have been performed (60, 61).

Heart disease

One million cases of Myocardial Infarction (MI) occurs annually in the United States and there are approximately 5 million patients with heart failure who have mortality rate of 20 percent (62). In a study in Bushehr in the south of Iran prevalence of CHD in men and women was 17.4% and 19.8% respectively. Crude rate of MI was 2.5% and a total of 4.9% of people suffered from angina (63), so there is an urgent need for novel treatments for repairment of ischemic cells and producing new cells. Cardiovascular disease is considered as a major cause of morbidity and mortality throughout the world. Cardiac muscle cells have little ability to repair themselves and current medications and angioplastic procedures cannot improve the contraction ability of cardiac muscles. Also because of limitations in organ donors for heart transplantation, this process cannot perform for all patients. Many studies were performed on various types of stem cells for treatment of MI, heart failure and ischemic cardiomyopathy. Martin-Rendon et al in their systematic review concluded that cellular therapy for MI is safe and cause 2.9 percent increase in LVEF, significant decrease in end diastolic volume of left ventricle and space of damaged area of myocardium but because of limitations in the number of trials these systematic review was unable to evaluate the effect of cell therapy on disability and mortality rate in patients (64).

Bone diseases

In normal situations after fracture, mesenchymal cells differentiate to chondrocyte and osteoblast and fracture will heal. Despite improvement in orthopedic surgical procedures, ununion is still a common problem that caused prolonged hospitalization (65).

Effect of mesenchymal cells derived from bone marrow and autologous bone marrow transplantation for treatment of ununion have been evaluated in animal studies as well as human clinical trials (66, 67).

Osteogenesis Imperfecta (OI) is a hereditary disorder that is characterized by bone fragility, bone density reduction and connective tissue disorders (68). After conducting animal studies (69), mesenchymal cells were examined in human studies (70). Hypophosphatasia is a rare disorder which results in metabolic bone disorder because of reduction of TNSALP¹ activity. Presentation of this disease in children is in form of rickets that often leads to death in the first few years of life because of weakness in respiratory muscles. So far specific drug has not been known for treatment of this disease. In study of Cahill et al., heterogeneous cells (provided from donor's bone pieces) were injected into three different locations intraperitoneally, subcutaneously and intravenously. It was expected that after replacement of these cells precursor cells would obtain ability of replacement and would differentiate to functional osteoprogenitor cells. Four months later graphies showed evidence of increasing mineralization and after seven years child was active and had a mild hypophosphatasia (71).

Renal failure

Renal failure is an important disease with mortality rate of 50-80 % (72). Due to restriction of donated organs, several preclinical studies which had promising results were conducted on using different types of stem cells in renal disease. Mesenchymal cells, Stem cells derived from adult human kidney and embryonic stem cells have been used for recovery of renal failure. Mesenchymal cells probably due to production of protective factors against cell death improve kidney healing in response to harmful agents. But these results have not been reported in chronic kidney damage. Also Embryonic stem cells and Stem cells derived from adult human kidney can produce tubular and glomerular cells (73-76).

Chronic wounds

Despite discovery of wound pathology and improvement of standard care, there are still basic problems in wound healing. 50% of chronic

¹Tissue-nonspecific isoenzyme of alkaline phosphatase

wounds that remain more than one year will be resistant to treatment (77). Different types of cells were evaluated in animal studies such as mesenchymal cells (in different forms for example spray in combination with thrombin or fibrin on wound (78), intradermal injection around the wound (79) or systematic injection (80) accelerated wound healing and made granulation tissue), collagen gel in combination with stem cells derived from adipocytes (decreased wound size and accelerated reepithelization) (81).

Graft-Versus-Host Disease

Graft-Versus-Host Disease (GVHD) is one of the complications of hematopoietic Stem Cell transplantation. In 50-80% of cases these patients can be treated by corticosteroids. For those who do not respond, new procedures such as mesenchymal transplantation have been proposed (82). Mechanism of mesenchymal cells against GVHD is still unclear. This effect could be due to factors such as IL-6 or TGF- β and cell to cell connection, MSC can be effective directly through the T-cell or indirectly through other immune cells such as dendritic cells or natural Killer Cells. In addition to animal studies these cells also have been evaluated in humans (83, 84).

Sepsis

Sepsis is a systemic inflammatory response to infection and one of the major causes of morbidity and mortality with an unclear pathophysiology (85, 86). Stem cells can be used in treatment of sepsis due to their characteristics such as modulation of inflammatory response and reduction of cellular apoptosis (87). Some of the studies reported bone marrow derived mesenchymal stem cells and embryonic stem cells act against edema and inflammation in sepsis (88, 89).

Respiratory Diseases

Chronic Obstructive Pulmonary Disease (COPD), Progressive airway obstruction and symptoms of dyspnea, cough, and sputum are the major characteristics of COPD (90). World Health Organization (WHO) reported that 210 million people have moderate to severe COPD. It is predicted

that COPD will become third major cause of death in the year 2030(91). In 2008 Scientists in China injected mesenchymal stem cells from male rats to female rat model of emphysema. Emphysematos changes in recipient female rats improved in comparison with control group (92). Xu et al performed a trial on adult human mesenchymal cells in patients with acute myocardial infarction. Forced Expiratory Volume in 1 second and forced Vital Capacity was improved in patients' undergone MSC injection (93).

Asthma

Ten percent of patients with asthma have severe refractory asthma that despite optimal standard treatment cause severe chronic symptoms and contributes to major portion of the health care costs of asthma. Nemeth et al. in 2010 injected mesenchymal stem cells into a ragweed induced mouse asthma model. During the antigen challenge, these cells because of immunomodulatory capacities inhibit eosinophil infiltration and excess mucus production in the lung, lower levels of Th2 immunoglobulins and IL-4, IL-5, and IL-13 in bronchial lavage (94).

Stem Cell Transplantation for Treatment of Diabetes Mellitus

Type 1 diabetes mellitus is an auto immune disorder which leads to destruction of pancreatic β cells (1). It has been proved that genetic susceptibility is effective in this process. Several polymorphism genes play role in the risk of type 1A diabetes including, HLA - DQalpha, HLA - DQbeta, HLA-DR, preproinsulin, the PTPN22, CTLA - 4, interferon-induced helicase, receptor IL2 (CD25) and the lectin gene such as (KIA0035), ERBB3e) (2-6). Gene polymorphisms lead to pancreatic β cell damage and diabetes via environmental factors. Presence of CD4 + T cells is essential in this process. Island Cell Autontibodies (ICAs) are the first markers in the serum of patients with polyendocrine immunodeficiency and 85 percent of newly diagnosed diabetic patients are positive for ICAs (95, 96).

So far various drugs and immune regulators have been used to reduce the destruction of beta cells

in diabetes type 1 alone or as combinations, through the immune system (97, 98). For this purpose in 1989 dexamethasone and azathioprine were used in 46 patients. Although level of C-Peptide increased, only in three of them recovery remained for one year (99, 100). Next treatments that were used for treatment of diabetes include MMF (mycophenolatemofetil) (100), cyclosporine (101, 102), antibodies against CD3 (103, 104), Rituximab (105), Thymoglobulin or antithymocyte globulin (106-109), GAD56 immunotherapy (106-111), bacillus Calmette-Guerin (106-112), Peptide derived from DiaPep 277 (113), Immunotherapy DAB486-IL2, donor splenocytes (114), inhibitor of TNF- α (115) and interferon α (116). Although some of these studies had positive results in adjustment of immune system, reduction of immunological marker levels and increase of C-Peptide, lots of unwanted drug side effects have been reported.

Considering effects of stem cells in immune system modifying and differentiation ability of these cells into specific cells, treatment with stem cells in various diseases, particularly autoimmune diseases has been interested researchers. In this section we aim to determine human trials of stem cells transplantation which have been conducted in treatment of diabetes.

Mesenchymal Stem Cells

In 2009, Bhansali et al. in India injected autologous mesenchymal stem cells to 10 patients with type 2 diabetes that did not respond to oral drugs and were treated by insulin. In 7 patients insulin dosage decreased to 75% and 3 patients became insulin free although in 1 of these patients this condition continued for a short period of time. This trial also caused decrease of HbA1c, increase of C-Peptide and weight loss and normalized lipid levels. No side effects were reported (117).

Also a clinical trial on the effect of mesenchymal stem cell therapy in type 1 diabetes have been performed at Endocrine & Metabolism Research Institute of Tehran University of Medical Sciences (Irct ID: IRCT138810271414N8).

Hematopoietic Stem Cells

Couri et. al in Brazil examined effects of autologous nonmyeloablative hematopoietic stem cell transplantation (HSCT) in two phases on 23 patients with type 1 diabetes aged 13-31 years. The duration of disease in these patients were 6 weeks and their diseases were confirmed by measuring serum level of anti-glutamic acid decarboxylase antibodies. Within 7 to 58 months of follow up, 20 patients who did not have previous ketoacidosis and did not receive corticosteroids became insulin free. In twelve of them this status continued for average of 31 months and eight others required low-dose insulin (0.1 to 0.3 units/kg). In group which became insulin free, HbA1c decreased to less than 7.0 % and average area under the curve of C-peptide increased significantly from 225.0 (75.2) ng/ml to (90.3) 785.4 ng/ml. Two, three and 9 patients developed bilateral nosocomial pneumonia, late endocrine dysfunction and oligospermia respectively and no mortality was observed (118).

In 2007 another group in Brazil supervised by Voltarelli performed the similar study on 15 type 1 diabetic patients. Within 7 to 36 months follow-up, 14 cases became insulin free (The period of this status in 1 patient was for 35 months, in 4 for 21 months, in 7 patients for at least six months and in two patients for 1 and 5 months). Among these 14 patients, one patient required insulin one year after AHST. Six months after transplantation, the mean total area under the curve of C-peptide levels increased significantly and was steady at the 12 and 24 months. Also after six months glutamic acid decarboxylase antibody levels went down and in 12th and 24th months remained constant. The serum levels of HbA1c in 13 out of 14 patients were less than 7 %. Culture-negative acute bilateral pneumonia and hypothyroidism and hypogonadism were the side effects but no mortality was observed (119). To determine whether this effect is because of changing the diet and lifestyle or beta cell function C-peptide level of these 15 patients and 8 additional patients were measured after 7 to 58 months. They reported that 20 out of 23 patients became insulin independent. 12 of them remained insulin free for 31 month and 8 patients

regained insulin dependence. In all of these 20 patients area under the curve of C-peptide increased (118).

In 2009 Bulum et al. transplanted autologous peripheral blood stem cells (PBSC) in 132 patients that 101 of them were suffering from refractory non-Hodgkin's lymphoma and 31 patients had Hodgkin disease. In 86 of them (65.6%) averagely six days after the transplantation fever and neutropenia occurred. All 10 patients with diabetes who were in the population under the study of transplantation of autologous peripheral blood stem cells developed febrile neutropenia. These patients compared with non-diabetics had the higher incidence of serious infections (60% in diabetics patients versus 30.3% in non-diabetics). Also it was showed that median time in defervescence was four days in diabetic patients versus 2 days in non-diabetics. *Staphylococcus epidermidis* was isolated as the most common pathogen. They concluded that serious complication of autologous peripheral blood stem cell transplantation is infection. Therefore, appropriate antimicrobial therapy according to microbiological epidemiology is essential after transplantation (120).

Ethical Challenges of stem cell transplantation

Intentional production, use and destruction of human embryos make stem cell therapy as a morally controversial issue. There are different opinions about moral status of this therapy. In the "conceptionalist" view embryo is considered as a person while on the other side of spectrum embryo is not considered as a person. There are lots of opinions between these extremes.

On the one hand, in the conceptionalist view, since it is believed that embryos have the potential to become a human being, extraction of stem cells from blastocyst is like extracting organs of a baby to save others' lives. These people have the same opinion about fertility treatments that involve production and discarding excess embryos.

Some people believe that moral status of embryos increases during their development and when they are born they reserved complete respect. So embryos need to be protected but not the same as

fully developed babies. This argument offers acceptable reasons for using embryos in therapeutic researches.

Another argument points out that development of embryo consists of different steps. Embryo has the potential to become one individual or more at the first 14 days of development but after that it can only develop in to one individual, so before 14 days of development they can be used for researches but after 14 days moral issues outweighs the interests of others.

Some people believe that because the potential of producing a baby has been removed from human embryonic stem cells they should not be considered as human embryos. But others may argue that they can change into a human being if they were built in to a cellular background with the ability of making extra-embryonic tissues.

There are also different arguments about creating embryos for research purposes. Since stem cells that are derived from excess embryos can cause immune rejection, some scientists believe that research cloning to create an embryo in order to create genetically identical cells will help avoid immune rejection. 'Fetalist' prospective focuses on the moral value of embryo and 'feminist' prospective focuses on the interests of candidate oocyte donors.

There also other principles about ethical issues of stem cell research such as proportionality, slippery slope and subsidiarity principle which enter the moral debate. The use of human embryonic germ cells from primordial germ cells of dead fetuses is morally more acceptable than the instrumental use of living pre-implantation embryos.

Using adult stem cells has been increased especially in animal model systems since the 1960s. Usage of these cells is not accompanied with moral issues and some scientists believe that they have sufficient ability of differentiation but others believe that their differentiation and proliferation capacity is more limited than that of embryonic stem cells.

Other ethical challenge is based on the fact that stem cell researches are very expensive and health care resources could be devoted to other more important health problems (121).

Conclusion

Stem-cell transplantation may offer potentially curative treatment for various hitherto incurable considered medical conditions in different branches of medicine. In endocrinology, the technology has demonstrated significant reduction in daily insulin requirement and increase in the blood C-peptide levels which may herald a cure for the disease in the future. However, there are ethical concerns and technical hurdles which need to be addressed in order for the technology to promise a definite cure for diabetes.

Ethical considerations

Ethical issues (Including plagiarism, Informed Consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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