Stem Cell Therapy in Treatment of Different Diseases

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Abstract- Stem cells are undifferentiated cells with the ability of proliferation, regeneration, conversion to differentiated cells and producing various tissues. Stem cells are divided into two categories of embryonic and adult. In another categorization stem cells are divided to Totipotent, Multipotent and Unipotent cells.
So far usage of stem cells in treatment of various blood diseases has been studied (such as lymphoblastic leukemia, myeloid leukemia, thalassemia, multiple myeloma and cycle cell anemia). In this paper the goal is evaluation of cell therapy in treatment of Parkinson's disease, Amyotrophic lateral sclerosis, Alzheimer, Stroke, Spinal Cord Injury, Multiple Sclerosis, Radiation Induced Intestinal Injury, Inflammatory Bowel Disease, Liver Disease, Duchenne Muscular Dystrophy, Diabetes, Heart Disease, Bone Disease, Renal Disease, Chronic Wounds, Graft-Versus-Host Disease, Sepsis and Respiratory diseases. It should be mentioned that some disease that are the target of cell therapy are discussed in this article.

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Introduction

What are stem cells? Stem cells are non-differentiated cells that have the ability of proliferation, regeneration, conversion to differentiated cells and tissue production. Regeneration means that these cells have the ability of asymmetric division which one of the resulting cells remains as stem cell while another cell, which is called daughter cell, becomes one cell of germ layer. Stem cells may remain inactive for a long time till they 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 that is in the 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, some times 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 into 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 adult or non-embryonic stem cells but more accurate word for them is "somatic stem cells" because these cells also exist in children and umbilical cord. They are divided 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 stem cells. One of the most important advantages of adult stem cells over embryonic stem cells

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Table 1. Different categories of stem cells.

Cell type	Definition
Totipotent cell	capability of differentiation into all cell types
Pluripotent cell	capability of differentiation into cells which are placed in fetal layers
Multipotent cell	capability of differentiation into cells of specific categories (in fetal layers)
Unipotent cell	capability of differentiation into only one type of cell and it is different from non-stem cell because of ability of regeneration

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

Different types of stem cells are shown 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 cells will be called as progenitor cells or stem cell-like cells that have the capability of regeneration (6).

Stem cell therapy has been evaluated in various blood diseases (such as lymphoblastic leukemia, myeloid leukemia, thalassemia, multiple myeloma, cell cycle anemia). The aim of this review is to evaluate cell therapy in other diseases.

Parkinson

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

Levodopa can improve the symptoms, but it can not prevent neurons from destruction, so in long - term its effects will be reduced or its side effects will appear (10). Today cell therapy is considered as a novel treatment and different types of cells have been studied for this purpose such as:

1) Embryonic stem cells: These cells have the ability of differentiation to neural stem cells and subsequently dopaminergic neurons, but they have short survival time. in a research by Sonntag et al. in 2006 showed that combination of Noggin that is a bone morphogenic protein antagonist with stromal cells can increase production of progenitor neouroepithelial cells that have the potential of differentiating to dopaminergic neurons. Unfortunately, usage of these cells may result in teratoma (11). There is no a human study in this field.

2) Mesenchymal cell: Venkataramana et al in 2010 injected mesenchymal cells into inferolateral ventricular area in 7 parkinson patients and observed significant improvement in symptoms such as facial gestures, gait and freezing episode. In two patients, dosage of Parkinson medication was significantly reduced .No side effects were observed in these patients (12).

3) Induced pluripotent stem cells (iPSC): These cells are capable of differentiation to neural progenitor cell (NPCs) and production of neurons and glial cells in culture. Wernig *et al.* in 2008 injected these cells into rat model of Parkinson and observed a significant behavioral improvement (13), but use of these cells may be associated with tumors (14).

4) Fetal neural stem cells: In study of Parish and his colleagues, transplantation of these cells to mouse model of parkinson disease led to significant cellular and functional improvement and they did not report any type of tumor (15).

5) Stem cells derived from adult brain: Tegmental neural stem cells in adult mice at the presence of growth factor developed functional neuron cells, including astrogelia, oligodandrogelia and neurons which have cholinergic and gabaergic markers in trial of Hermann *et al.* (16).

6) Mature multi potent stem cells: Dezawa et al reported that use of mature multipotent stem cells in mouse model of parkinson improved apomorphine-induced rotational behavior and regulated step and paw reaching test (17).

Amyotrophic lateral sclerosis

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 (18). Recently replacement of various types of stem cells has been suggested for treating this disease:

1) Replacement of motor neurons: ALS is a progressive disease that impairs movement of the diaphragm and results in death. Since the appearance of the effect of replaced motor neurons in humans requires long time, there is a restriction in usage of these cells (19).

Xu *et al.* in 2009 indicated that replacement of human neural stem cells in mice resulted in their differentiation to neurons with GABAergic phenotype that made localized synapses and could cause protective effects for motor neurons and so improved the symptoms (20).

2) Astrocytes replacement: ALS patients have astrocyte impairment in adition to defects of motor neurons. Lepore et al. in 2008 injected precursor of lineage-restricted astrocyte called Glial-Restricted Precursors (GRPs) intosuperoxide dismutase 1

SOD1 mice and observed that these cells increased survival, reduced motor neuron damage and decreased motor function of anterior limbs and slowed down respiratory disorders (21).

3) Hematopoietic stem cells: Although these cells can potentially differentiate to various types of immune cells and microglia but in the study conducted by Appel *et al.* in which haematopoietic stem cells were injected into 6 patients with ALS, no clinical improvement was observed (22).

4) Mesenchymal cell: Suzuki and his colleagues injected mesenchymal stem cells into muscles of mice with familial ALS and observed that these cells caused glial cell line-derived neurotrophic factor secretion increased the number of neuromuscular connection and motor neuron cell bodies in the spinal cord and prolonged survival for 28 days (23).

Alzheimer

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 disease. Cell therapy is one of the treatments. For this purpose different stem cells have been used such as:

-Neural stem cells: Neural stem cells have the ability of differentiation to neurons, astrocytes and oligodendrocytes. Xuan et al. marked neural stem cells of hippocampus and glial cell-derived neural stem cells and injected them into basal part of forebrain in 2 groups of mice. They observed that the number of cholinergic neurons in the group which received neural stem cell was significantly higher than the group that received glial cells. There were no significant differences in cognitive ability between the mice that received glial cells and those which received neural stem cells. But there was a significant difference in cognitive ability of mice which were injected neural stem cells and mice with lesions which did not receive any injection (24).

-Mesenchymal stem cells: Lee *et al.* injected mesenchymal stem cells derived from human umbilical cord into Alzheimer's mice and observed that markers of glial activity, oxidative stress and apoptosis were decreased in mouse brain. Also cognitive abilities and learning and memory in mice were returned (25).

-Neural precursor cells derived from embryonic stem cells: Moghaddam *et al.* reported that injection of neural precursor cells derived from embryonic stem cells or cells that subsequently become cells with cholinergic phenotype caused significant improvement in behavioral disorder and memory in mice and there was no sign of tumor (26).

Stroke

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 neuronal regeneration process. Animal studies and several preclinical trials confirm efficacy of cell therapy in functional improvement after stroke. Although the functional 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 and stimulation of host brain plasticity and use of internal progenitors are its possible effects. Different types of cells that have been used for this purpose are summarized in Table 2.

Spinal cord injury

Spinal cord injury is one of the severe neurological damages that leads to loss of neuron tissue and subsequently loss of sensory and motor functions. 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: Kerr *et al.* injected oligodendrocyte progenitor cells derived from human embryonic stem cells into rats with spinal cord injury. Results showed that these cells had at least 8 days survival after injection and increased neurological responses in treated mice compared with control mice (35), but since these cells can cause tumor, use of them in human studies is ethically challenging (36).

-Neural stem cells: Many studies have been conducted on using neural stem cells in spinal cord injury. Yan *et al.* injected neural stem cells derived from human fetal spinal cord after culturing, into the spinal cord of healthy rats and rats with spinal cord injury and

observed that these cells differentiated into neurons and created axons and synapses and connected widely to host motor neurons. Less than 1/10 of the transplanted neurons were differentiated into oligodendrocytes (37). Song *et al.* conducted a study on the best time for use of these cells and concluded that the acute phase is the best time for cell transplantation (38).

-Olfactory Ensheathing Cells (OECs): OECs are special glial cells that exist only in olfactory system and support production of olfactory neurons (39). Lopez *et al.* examined the use of these cells on rats in acute phase and after a week in the area of spinal cord injury in the thoracic level 8(T8). OEC transplantation improved performance and behavior and histologically caused axon's regeneration. This positive result in the mice that were treated in the acute phase was better than those mice that were treated with delay (40).

-Mesenchymal cells: The effect of these cells in animal studies and clinical trials has been evaluated.

Table 2. Different types of stem cells that have been used in treatment of stroke.

Type of cell	Effect	Type of Study (animal / human)	Reference
Neural progenitor cells derived from human Embryonic stem cells	Neural stem cells derived from human embryonic stem cells, differentiated to neurons, oligodendrocytes and astrocytes.	animal	(27)
Neural progenitor cells derived from embryos	Human Neurosphere cells cultured in vitro improved neurological activity in mice. Also some synapses between neurons derived from human embryonic stem cells and host neurons were produced.	animal	(28)
Immortalized cell lines	Transplantation of cells, that were immortalized through connection of transgene c-mycERTAM and then cultured in the presence of 4-hydroxy tamoxifen, to animal model resulted in reduction of functional impairments	animal	(29)
Stromal cells of human adipose tissue	Injection of stromal cells of human adipose tissue into the left ventricle of mouse brain showed that these cells have ability of survival, migration, and functional improvement after stroke.	animal	(30)
Peripheral blood cells	The injections of peripheral blood stem cells as well as cord blood stem cells in mice resulted in decrease of hyperactivity due to stroke and progression of motor asymmetry.	animal	(31)
Blood cells of human umbilical cord	Blood cells of Human umbilical cord after intravenous injection into rat brain, had the ability of survival, migration, and improvement of performance after stroke	animal	(32)
Mesenchymal cells	Intravenous administration of human mesenchymal cells to mice improved performance and reduced infarction rate and neuroprotectine.	animal	(33)
Bone marrow stromal cells	Injection of bone marrow stromal cells increased axonal plasticity that can cause neurological functional improvement.	animal	(34)

In the study of Cho and his colleagues, mesenchymal stem cells and differentiated mesenchymal stem cells derived from bone marrow used for evaluation of performance improvement in mice with spinal cord injury. Although transplantation of mesenchymal cells improved motor function, but in the rat that had been taken differentiated mesenchymal stem cells, Basso-Beattie-Bresnahan (BBB) scores were higher and N1 and P1 latency were shorter compared with the control group which had been treated with phosphate-buffered saline (41). In a clinical trial performed by Yoon and his colleagues effect of mesenchymal cells in three phases of acute (14 days after injury), sub acute (14 days to 8 weeks after injury) and chronic (more than 8 weeks after the injury) were evaluated. There was not any report of side effects after injection. AIS scores (Spinal Injury Association Impairment Scale) in acute and sub acute group improved up to 30 percent whereas in the chronic group did not change (42).

-Progenitor Stem Cells: Keirstead and his colleagues injected progenitor oligodendrocyte cells derived from human embryonic stem cells 7 days or 10 months after spinal cord injury into adult mice and observed that in both cases, cells survived and then differentiated to oligodendrocytes. In mice that were taken cells 7 days after spinal cord injury, increase of remyelination and improvement of motor activity was observed whereas in the other group these effects were not observed (43).

Multiple sclerosis

Multiple Sclerosis (MS) is a chronic inflammatory and degenerative disease in central nervous system that is probably associated with autoimmunity of CD4 T-cells (44). Immunomodulator drugs are current treatment of MS, but long term effect of these drugs is so limited that only 30 percent of patients benefit from these drugs in long-term (45,46). Bcause of immunoregulation ability stem cells can be useful for these patients. Cells which have been used for this purpose are listed below:

- Embryonic stem cells: Aharonowiz *et al.* injected human embryonic stem cells into animal model of MS, and they concluded that these cells improve clinical symptoms via immunosuppressive neuroprotective mechanism, not by remyelination mechanism (47).

- Adult neural stem cells: Politi *et al.* monitored gathering of marked neural stem cells after intravenous injection to animal model of MS. 24 hours after transplantation these cells were detected in 80 percent of demyelination area, and remained up to 20 days after injection, but they were not detected in normal areas of brain (48).

- Mesenchymal Stem cells: In trial of Barhum *et al.* mesenchymal cells differentiated into Neurotrophic Factor-producing Cells (NTFCs) in vitro. Afterwards mesenchymal cells and NTFCs were injected into ventricles of animal model brain. These cells through regulating of immune system and prevention of oxidative change delayed onset of clinical symptoms and increased survival (49). Mohyeddin Bonab *et al.* injected cultured mesenchymal cells intrathecally into 10 multiple sclerotic patients with Expanded Disability Status Scale (EDSS) 3.5 to 6. After an average of 19 months follow-up, EDSS of one patient decreased, four patients had no change and in 5 patients the disease progressed. Also in sensory, pyramidal and cerebellar evaluation, six patients had been recovered some degree, one patient had no change and disease progressed in 3 patients (50).

Radiation-induced intestinal damage

Radiotherapy after pelvic or abdominal tumors may result in adverse effects such as intestinal mucosal damage, loss of villi, mucosal atrophy and intestinal dysfunction (51,52). 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 (53-56). Modified mesenchymal cells by CXCR-4 (the receptor for SDF-1=stromal cell- derived factor 1) were evaluated in a case of radiation- induced enteropathy by Zhang *et al.* It was observed that these cells can significantly improve intestinal permeability and histopathological damage (52).

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 immunoregulatory cells,and also because of the ability of transdifferentiation and cell fusion it seems that they have a positive effect in improvement of these diseases (57).

In 1993 Drakos *et al.* for the first time reported that in 1 patient with blood malignancy who had taken autologous blood stem cell transplantation, symptoms of Crohn disease improved (58). These studies continued. In 2005, Oyama *et al.* conducted 1st phase of hematopoietic stem cell transplantation in 12 patients with recurrent Crohn disease and Crohn's disease by activity index (CDAI) between 250- 400 and concluded

that use of these cells is safe and improves symptoms of patients. After an average of 18.5 months follow-up, only 1 patient had a recurrent active disease (59).

Cassinotti *et al.* in the first and second phases of a pilot study injected autologous hematopoietic stem cells without selection for CD34 to four patients and concluded that these cells are safe and after an average of 16.5 months follow-up, in 3 / 4 of patients without any other treatment the disease has been controlled (60). Phase 3 clinical trial of using these cells is running (ClinicalTrials.gov Identifier: NCT00297193)

Use of mesenchymal cells in the treatment of this disease had promising results. Gonzalez *et al.* injected mesenchymal stem cells derived from human fat into mice with colitis. These cells improved symptoms, prevented patients from weight loss, diarrhea and inflammation and increased survival (61). Garcia- Olmo *et al.* in the first Phase of clinical trial evaluated safety and efficacy of using mesenchymal cells of adipose tissue for treatment of 5 patients with Crohn fistula. 8 fistula lesions were studied in these patients. After eight weeks external orifice of six fistulas were closed, two fistulas were incompletely closed and use of these cells had no complications (62).

Liver diseases

Nowadays stem cell transplantation has 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 (63-67). Also laboratory studies have shown that primary hepatocytes can be replaced in liver, spleen, peritoneal cavity and other sites outside the liver (67). A number of human studies about the use of stem cells in cirrhotic patients have been performed such as:

- Gordon *et al.* in 2006 injected autologous CD34 cells into five patients through hepatic artery or portal vein. This intervention resulted in decrease of bilirubin, improvement of albumin level and ascites in 4, 3 and 1 patients respectively and no side effects were reported (68).

- Terai *et al.* in 2006 evaluated effect of injection of bone marrow mononuclear cells through peripheral vesseles in patients with cirrhosis and observed significant improvement in albumin level, total protein and Child-Pugh score (69). Also In study of Lyra *et al.* that 10 male patients with cirrhosis were injected autologous cells derived from bone marrow through hepatic artery, it was shown that injection of these cells in patients with advanced cirrhosis had no side effect and improved liver function tests such as bilirubin and International Normalized Ratio (INR)and increased albumin (70).

- Gupta *et al.* injected autologous stem cells into 12 children with congenital cirrhosis through hepatic artery, portal vein or hepatobiliary radicals. 5 patients died due to cirrhosis. From 7 remaining patients, 4 patients recovered from cholangitis. In 3 patients liver stiffness and in 6 patients liver function was improved (71).

- Phase 1 trial of Mohammad Nejad *et al.* has shown safety of autologous mesenchymal cell injection. In another study conducted by the same group, in three out of four patients, liver function tests and general appearance significantly improved, but one patient died because of radiocontrast nephropathy that caused hepatorenal Syndrome type 1 (72,73).

Duchenne muscular dystrophy

Duchenne Muscular Dystrophy is a recessive X-linked disease in which reduction of dystrophin presentation in sarcolemma of muscle fibers causes progressive muscle weakness (74,75). Different types of stem cells that have been used for the treatment of Duchenne disease are listed below:

- Myogenic progenitor cells: Evaluation of these cells in vitro and human trials showed that these cells can not potentially differentiate to muscle fibers containing dystrophin and recipient body makes antibodies against them so transplantation would be rejected (76-80).

-Satellite cells: These are cells which are located between basement membrane cells and sarcolemma of muscle fibers. Although theoretically it seemed that usage of these cells reduces immune rejection, but in vitro, animal and human studies showed that because of low potential ability of differentiation to muscle cells, also restriction in production of sufficient numbers of these cells, they can not improve clinical presentations (81-83).

- Bone marrow stem cells: Various studies have shown that injection of bone marrow stem cells, such as hematopoietic cells into immunocompromised mice, caused aggregation of these cells in muscle degeneration area, and they participated in healing process of muscle fibers and resulted in accumulation of satellite cells (78,84,85).

-Side population: These cells are the scarce skeletal muscle cells. Recent animal studies have shown that these cells in fetal skeletal muscle cells act as paracrine cells and secrete factors that stimulate

proliferation of myogenic cells in adjacent regions (86,87).

-Mesoangioblasts: Mesoangioblasts are multipotent progenitor cells of mesoderm tissue. Animal studies have shown that all differentiated mesoangioblasts are able to make myofibrils containing dystrophin and increase muscles contraction (88,89).

- Pericytes: Pericytes are progenitors of mesenchymal cells that migrate from their place in arterial wall during damage and produce mesenchymal cells. Injection of these cells in mice produced a large number of muscle fiber cells (90,91).

-CD133+cells derived from blood or muscle: CD133+cells derived from blood or muscle after arterial or muscular injection in mice obtained the ability of differentiation to muscle or blood cells. Since these cells have no side effects and can increase number of capillaries per muscle fibers, they can be used in Duchenne patients (83,92,93).

Diabetes

Prevalence of diabetes in the world is increasing rapidly. It is predicted that by the year 2030, 366 million people will have diabetes (94). About 7.7 percent of Iranian population that is equal to more than the 2 million people are suffering from diabetes (95). In the year 2000 burden of diabetes in Iran was estimated to be 306440 years (96). Life-long assessments of blood sugar, daily insulin injections and limited nutrition diets are factors that influence quality of life in these patients. Moreover, diabetes complications are a major burden on the national health budget (97). One of the treatment strategies for these patients is pancreatic islet cell transplantation (98) but in this method there is a limitation of donor organs as well as low possibility of becoming insulin free (99,100).

Stem cell therapy is another strategy. Different types of stem cells for diabetes treatment have been studied such as:

-Embryonic stem cells: The first report of insulin producing cells from mouse embryonic stem cells was published in 2000 by Soria *et al.*, but these cells had short life (101). More studies have been performed in this field and via manipulation of culture, separating Nestin presenting cells, adding inhibitors of phosphoinositide kinase also using pdx1 and pax4 that are translation factors associated with beta cells, promising results were obtained (102-105).

-Mesenchymal cells: Several laboratory and clinical studies showed that mesenchymal cells have immunomodulation ability through regulation the activity of Bcell, Tcell, Natural Killer cells and cytokines such as TGFβ and interleukin 10 (106). These cells could potentially differentiate to insulin producing cells in special cultures. Different types of mesenchymal cells which show the ability of differentiation into insulin-producing cells in vitro include: mesenchymal cells derived from bone marrow (107,108), adipose tissue (109), Cord (110)and mesenchymal cells of pancreas (111,112). Usage of bone marrow derived mesenchymal cells and umbilical cord mesenchymal cells had positive effects in animal studies and improved blood glucose status (113-116). A clinical trial on mesenchymal cell therapy in type 1 diabetic patients is already running in Endocrine and Metabolism Research Institute of Tehran university of Medical Sciences.

-Other types of cells: different types of cells such as skin fibroblast cells (117), human neural progenitor cells (118), hepatic oval cells (119) and placenta- derived stem cells (120) in special conditions have the potential of differentiation into insulin producing cells.

Stem cell therapy has been used for treatment of some kinds of diabetic complications such as diabetic foot. Using fetal CD 133+cells (121), autologus bone marrow stem cells (122), autologus biograft and mesenchymal stem cells (123) and autologus peripheral blood mononuclear cells (124) had promising results.

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 (125). 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 Myocardial infarction (MI) was 2.5% and a total of 4.9% of people suffered from angina, so there is an urgent need for novel treatments for repairment of ischemic cells and producing new cells (126). 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 can not improve the contraction ability of cardiac muscles. Also because of limitations in organ donors for heart transplantation, this process can not perform for all patients. Many studies were performed on various types of stem cells for treatment of MI, heart failure and ischemic cardiomyopathy (Table 3).

Martin-Rendon *et al.* in their systematic review concluded that cellular therapy for MI is safe and cause 2.9 percent increase in Left ventricular ejection fraction

(LVEF), significant decrease in end diastolic volume of left ventricle and space of damaged area of myocard 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 (127).

Bone diseases

Non ununion

In normal situations after fracture, mesenchymal cells differentiate to chondrocyte and osteoblast and fracture will heal. Despite improvement in orthopedic surgical procedures, Non ununion is still common problems that cause prolonged hospitalization (139).

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 (140). For example in Marcacci *et al.* study, bone marrow stromal cells with macroporous bioceramics were grafted in defective areas in 4 patients with large bone diaphysis disorder during surgery, and it showed evidence of bone healing in radiography and CT (141).

Osteogenesis imperfecta

Osteogenesis Imperfecta (OI) is a hereditary disorder that is characterized by bone fragility, bone density reduction and connective tissue disorders (142).

After conducting animal studies (143), mesenchymal cells were examined in human studies. In study of Horwitz *et al.* mesenchymal cells derived from labeled genetic bone marrow of donors, were injected twice into 6 children with severe OI who had been treated with normal bone marrow transplantation previously. These patients in comparison with the same patients who were matched in age and sex and had not received any treatment, improved 60 to 94 percent (average 70 percent) and there was no side effect (except urticaria after the second injection that was seen in one patient) (144).

Hypophosphatasia

Hypophosphatasia is a rare disorder which results in metabolic bone disorder because of reduction of tissue-nonspecific alkaline phosphatase (TNSALP) activity.

Table 3. Different kinds of stem cells that have been used for treatment of cardiac diseases.

Type of cell	Effect	Type of study (animal/human)	Reference
Embryonic and umbilical cord stem cells	Umbilical cord includes various types of stem cells such as mesenchymal and hematopoietic cells. In animal models using this type of cells, significant improvement in heart function was seen.	Animal	(128-130)
Hematopoietic stem cells	These cells are able to be replaced in damaged myocard, but it has not been determined whether these cells have the potential of changing into endothelial cells and cardiomyocytes or they just join to cardiomyocytes.	animal	(131)
Mesenchymal stem cells	Previous studies had paradoxical results about survival of these cells after the injection, so further studies are required for clinical use of these cells.	animal	(132-134)
Heart Stem Cells	Although these cells have higher potential of proliferation, but this is not adequate in extensive injuries such as MI.	animal	(125)
Skeletal myoblasts	Although these cells were the first cells that have been injected into ischemic myocard, clinical trials results indicated that these cells do not improve heart function and even may resulted in arrhythmia.	human	(135, 136)
Progenitor cells derived from bone marrow	Injection of Progenitor cells significantly increased left ventricular ejection, improved infarct area movement and decreased end systolic volume.	human	(137)
Mononuclear cells derived from bone marrow and blood	There have not been reported any positive effect and they may result in arrhythmia.	human	(138)

Presentation of this disease in children is in form of rickets that often leads to death in the first 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 intraperitonealy, 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. 4 months later graphies showed evidence of increasing mineralization and after seven years child was active and had a mild hypophosphatasia (145).

Kidney disease

Kidney is a highly differentiated organ and its cells have limited potential for proliferation so kidney have the least possibility of regeneration among organs of body but in clinic renal regeneration can be seen for example we can see the renal function improvement after acute renal failure (146). Renal failure is an important disease with mortality rate of 50-80 % (147). 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. Different types of cells that have been used for this purpose include:

-Mesenchymal cells: Animal studies have shown that mesenchymal cells probably due to production of proreparative growth factors and protective factors against cell death improve kidney healing in response to harmful agents. But these results have not been reported in chronic kidney damage (148).

-Stem cells derived from adult human kidney: Special types of stem cells are found in bowman capsule that are called Adult Parietal Epithelial Multipotent Progenitors (APEMPs), which can produce tubular and glumeral cells. Mazzinghi *et al.* injected APEMPs to mice 4 and 20 hours after glycerol injection and reported improvement of renal function, reduction of BUN level and necrotic area (149,150).

-Embryonic stem cells: Kim *et al.* evaluated usage of embryonic stem cells in animal models.Embryonic stem cells after culturing at first produced embryonic body and after another culture with increased concentrations of retinoic acid, activin A and bone morphogenic protein, produced kidney progenitor cells. Injection of these calls to developing kidney caused differentiation to tubular epithelial cells with 100% efficacy (151).

Chronic wounds

Despite discovery of wound pathology and improvement of standard care, there are still basic problems in wound healing. 50% of chronic wounds that remain more than one year will be resistant to treatment (152). Different cell types were evaluated in animal studies such as mesenchymal cells (in different forms for example spray) in combination with thrombin or fibrin on wound (153), intradermal injection around the wound (154) or systematic injection (155) accelerated wound healing and made granulation tissue), collagen gel in combination with stem cells derived from adipocytes (decreased wound size and accelerated reepithelization) (156). Liu *et al.* used hair follicle's micrografts in derm 12 days after burning and saw increase in reepithelization, improvement of stem cell reserves, increasing of hair growth and maturation of skin (157).

Also clinical trials have been conducted on using stem cells in patients with chronic wounds such as use of mesenchymal cell spray in combination with fibrin or thrombin on acute and chronic wounds by Falanga *et al.* (there was a significant correlation between the number of cells and reduction of wound area and leaded to decrease of pain and wound area) (139), topical application of mesenchymal cells in patients with chronic wounds by Badiavas and his colleagues (resulted in closure of wound, increase cellularity and dermal healing) (158).

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 (159). 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 (160).

In addition to animal studies these cells also have been evaluated in humans. Ringden *et al.* injected mesenchymal cells into eight patients with recurrent GVHD taking steroids and patients with chronic GVHD. No side effects were observed after injection. 6 patients were injected once and 3 patients were injected twice. In 6 patients GVHD was resolved. Survival rate of these patients was significantly higher than the patients who

did not respond to steroid and had not taken mesenchymal cells (161).

But in Arima study that cultured mesenchymal cells were injected intra arterially, only one of three patients had a partial improvement. In two other patients idiopathic pneumonia was made. This study concluded that a single arterial injection of mesenchymal cell is not effective as much as intravenous injection (162).

Sepsis

Sepsis is a systemic inflammatory response to infection and one of the major causes of morbidity and mortality with an unclear pathophysiology (163,164). Stem cells can be used in treatment of sepsis due to their characteristics such as modulation of inflammatory response and reduction of cellular apoptosis (165). Here we summarize examples of the researches on this field:

-Human Embryonic Stem Cell: Sophie *et al.* reported that injection of differentiated human embryonic stem cells significantly decreased lung inflammation and edema and produce TNF-α and interfrone-γ. In Mice that received transplantation the mortality rate was 50% whereas control group had mortality rate of 90%. Also it was shown that only ACE+ cells have anti inflammatory ability and can improve sepsis (166).

-Mesenchymal Stem Cells: Gupta *et al.* injected mesenchymal cells directly to the lung air spaces of mice 4 hours after the infection with Escherichia coli endotoxin. It was reported that these mice had less pulmonary edema, alveolar epithelial permeability, TNF-α and MIP-2 in the bronchoalveolar lavage and plasma and finally less severe endotoxin-induced acute lung injury and more survival (167).

-Another research group at Emory University in 2007 divided the mice which received injection of Escherchia-coli endotoxin in the peritoneum in to 4 groups. The first group was injected by the salin solution and bone marrow derived mesenchymal stem cells (BMDMSC), the second group by endothoxin and BMDMSC, the third group by endotoxin and mouse lung fibroblasts and the last group by only endotoxin. BMDMSC acted against edema and inflammation followed by endotoxin injection but after a couple of weeks donor cells were not detectable. They concluded that part of BMDMSC effects is due to generation of stem cell chemoattractants in the lung of the mice and being mobile (168).

Respiratory diseases

Chronic obstructive pulmonary disease (COPD)

Progressive airway obstruction and symptoms of dyspnea, cough, and sputum are the major characteristics of Chronic Obstructive Pulmonary Disease (COPD)(169). 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 (170).

-Mesenchymal stem cells: In 2008 Scientists in China injected mesenchymal stem cells from male rats to female rat model of emphysema. Emphysematous changes in recipient female rats improved in comparison to control group.Detection of Y chromosome and immunohistochemical staining for surfactant protein-C (SP-C) showed that Mesenchymal stem cells (MSCs) were present at recipient lungs, differentiated into type II alveolar epithelial cells and could decrease the alveolar cell apoptosis (171).

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 who received MSC injection (172).

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 (173). In conclusion, most of the studies have suggested that stem cells because of immunomodulatory capacities can be effective in control of immune-based diseases and stem cells differentiation ability may cause them as a new promising therapy for organ or tissue defect in the near future.

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