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# An Introduction of Stem Cell Therapy and Implication on Human life-A Review

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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 such as lymphoblastic leukemia, myeloid leukemia, thalassemia, multiple myeloma and cycle cell anemia. In this report the goal is evaluation of cell therapy in treatment of Parkinson's disease, Amyotrophic lateral sclerosis, Alzheimer, Spinal Cord Injury, Multiple Sclerosis, Liver Disease, Diabetes, Heart Disease, Bone Disease and Respiratory diseases.

Keywords: Stem cells; Human diseases; Cell Therapy; Medical application.

## I. Introduction

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 [1]. Stem cells are non- differentiated cells that have the ability of proliferation, regeneration, conversion to differentiated cells and tissue production. 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. 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. One of the most important advantages 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 [1, 2, 3].

Table: Different of category of stem cell

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

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 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 [4].

## II. Different type of diseases

### Parkinson Disease

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. Today cell therapy is considered as a novel treatment and different types of cells have been studied for this [5].

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. Unfortunately, usage of these cells may result in teratoma. There is not 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[6]. Noside effects were observed in these patients. 3) Induced pluripotent stem cells (iPSC): These cellsare 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, but use of these cells may be associated with tumors.

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.

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.

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.

**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. 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. 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.

2) Astrocytes replacement: ALS patients have astrocyte impairment in addition to defects of motor neurons. Lepore et al. in 2008 injected precursor of lineage-restricted astrocyte called Glial-Restricted Precursors (GRPs) into superoxide dismutase 1 mice and observed that these cells increased survival, reduced motor neuron damage and decreased motor function of anterior limbs and slowed down respiratory disorders.

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 hematopoietic stem cells were injected into 6 patients with ALS, no clinical improvement was observed.

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 [7].

**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. 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. 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 [3,4,5].

**Spinal cord injury**

Spinal cord injury is one of the severe neurological damages that lead 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. -Embryonic stem cells: Kerr et al. injected oligodendrocyte progenitor cells derived from human embryonic stem cells into rats with spinal

**cord injury.**

-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. -Olfactory Ensheathing Cells (OECs): OECs are special glial cells that exist only in olfactory systemand support production of olfactory neurons. 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. -Mesenchymal cells: The effect of these cells in animal studies and clinical trials has been evaluated. 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. -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 [5,6.9].

**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. 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. -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.

- 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. 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 [2, 4,6, 8].

**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. Also, laboratory studies have shown that primary hepatocytes can be replaced in liver, spleen, peritoneal cavity and other sites outside the liver. 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. -Terai et al. in 2006 evaluated effect of injection of bone marrow mononuclear cells through peripheral vessels in patients with cirrhosis and observed significant improvement in albumin level, total protein and Child-Pugh score. 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. -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 [7, 8, 9].

**Diabetes**

Prevalence of diabetes in the world is increasing rapidly. Life-long assessments of blood sugar, daily insulin injections and limited nutrition diets are factors that influence quality of life in these patients. 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. -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 TGFß and interleukin 10. These cells could potentially differentiate to insulin producing cells in special cultures. -Other types of cells: different types of cells such as skin fibroblast cells, human neural progenitor cells, hepatic oval cells and placenta- derived stem cells 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, autologus bone marrow stem cells, autologus biograft and mesenchymal stem cells and autologus peripheral blood mononuclear cells had promising results [5, 8,9].

**Heart disease**

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. 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 Left ventricular ejection fraction (LVEF), significant decrease in end diastolic volume of left ventricle and space of damaged area of myocardia but because of limitations in the number of trials this systematic review was unable to evaluate the effect of cell therapy on disability and mortality rate in patients [2,6, 10].

**Bone diseases**

**Osteogenesis imperfecta**

Osteogenesis Imperfecta (OI) is a hereditary disorder that is characterized by bone fragility, bone density reduction and connective tissue disorders. After conducting animal studies, 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, there was no side effect[ 1, 3,11].

**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. -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. Xu et al. performed a trial on adult human mesenchymal cells in patients with acute myocardial infarction. orced

Expiratory Volume in 1 second and forced Vital Capacity was improved in patients who received MSC injection [2, 4, 12].

**III. Conclusion**

Stem cells derived from all sources hold immense medical promises. Stem cell therapies have virtually unlimited medical application. While there are several barriers that need to be broken down before this novel therapy can be translated from lab to clinics, it is certain that the future is going to be exciting for all of us. We have moved on from the surgical model of care to the medical model and are likely to move onto the biological model of care. The need of the hour is high-quality research coupled with collaboration between basic scientists and the clinicians. A team effort engaging the expertise of the molecular biologists, immunologists, biomaterial scientists, cell biologists, matrix biologists, and are crucial in attaining the desired goal. Stem cell therapy is no longer science fiction. Stem cell therapy has brought in a lot of optimistic hope amongst researchers, doctors, and not to forget the patients who are the chief beneficiary of this innovation. Stem cells regenerate hope and not all that is happening in research is hype. Remember – "Hope is a prerequisite for any successful scientific innovation" And one day, very soon, stem cells will be introduced as an alternate or adjuvant in medicine.

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