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Stem Cell Therapy: A Novel Treatment for Various Diseases and Injuries

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ABSTRACT

Stem cells are one of the fascinating areas of biology today. Stem cells offer promise and have the potential to treat a number of conditions. All stem cells regardless of their source have three general properties: they are capable of dividing and renewing themselves for long periods; they are unspecialized and they can give rise to specialized cell types. There are many technical hurdles between the promise of stem cells and the realization of these uses, which will only be overcome by continued intensive stem cell research. Stem cell-based therapies are found to be significant in the management of various diseases like cancer, Diabetes mellitus, Age-related macular degeneration, Spinal cord injuries, etc. This review article discusses how to treat different types of diseases by stem cell (SC) therapy.

INTRODUCTION

Research on stem cells is advancing knowledge about how an organism develops from a single cell and how healthy cells replace damaged cells in adult organisms. This promising area of science is also leading scientists to investigate the possibility of cell-based therapies to treat disease, which is often referred to as regenerative or reparative medicine (1). Stem cells are one of the fascinating areas of biology today. Stem cells offer promise and have the potential to treat a number of conditions. However, the only stem cell treatment that has been scientifically proven is haematopoietic stem cell transplantation. All other medical stem cell treatments are currently unproven and have not yet been established as safe and effective (2).

Unique properties of stem cells:

Stem cells differ from other kinds of cells in the body. All stem cells regardless of their source- have three general properties: they are capable of dividing and renewing themselves for long periods; they are unspecialized and they can give rise to specialized cell types. Scientists primarily work with two kinds of stem cells from animals and humans: Embryonic stem cells and Adult stem cells, which have different functions and characteristics (1).

Types of stem cells:

1) **Adult stem cells**: Stem cells found in different tissues of the developed, adult organism that remain in an undifferentiated or unspecialized state. These stem cells can give rise to specialized cell types of the tissues from which they came.
2) **Embryonic stem cell:** Cells derived from the inner cell mass of developing blastocysts. An ES cell is the self-renewing, pluripotent and theoretically is immortal.
3) **Mesenchymal stem cell (bone marrow stromal cells):** Rare cells, mainly found in the bone marrow, that can give rise to a large number of tissues types such as bone, cartilage (the lining of joints), fat tissues, and connective tissue.
4) **Neural stem cell:** A type of stem cell that resides in the brain, which can make new nerve cells (called neurons) and other cells that support nerve cells (called glia). In adults NS cells can be found in very specific and very small areas of the brain where replacement of nerve cells is seen.

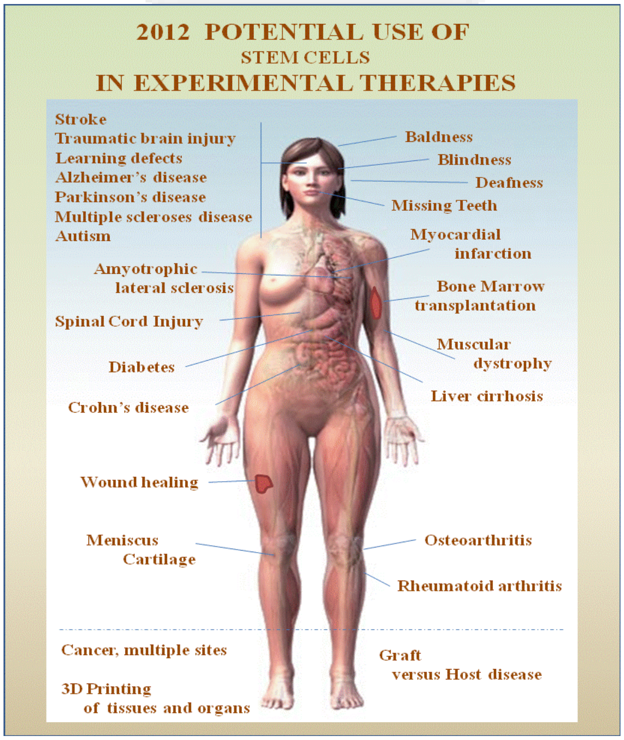
5) **Hematopoietic stem cells:** The precursors of mature blood cells that are defined by their ability to replace the bone marrow system following its obliteration (e.g. by g-irradiation) and can continue to produce mature blood cells (2, 16).

Stem Cell Therapy:

There are many technical hurdles between the promise of stem cells and the realization of these uses, which will only be overcome by continued intensive stem cell research. The following is a list of steps in successful cell-based treatments that scientists will have to learn to precisely control to bring such treatments to clinic. To be useful for transplant purposes, stem cells must be reproducibly made to:

- Proliferate extensively and generate sufficient quantities of tissue.
- Differentiate into the desired cell types.
- Survive in the recipient after transplant.
- Integrate into the surrounding tissue after transplant.
- Function appropriately for the duration of recipient's life.
- Avoid harming the recipient in any way (1).

Figure no: 1(60)



Medical uses:

1] Bone marrow (Stem Cell) transplant for Sickle Cell Diseases:

Bone marrow (stem cell) transplants have been used for the treatment and cure of a variety of cancers, immune system diseases, and blood diseases for many years. Bone marrow (stem cell) transplant is the only treatment available today that can cure sickle cell disease.

How does a bone marrow transplant work?

In a person with sickle cell disease, the bone marrow produces red blood cells that contain Hb S. This leads to the complications of sickle cell disease. To prepare for a bone marrow transplant, strong medicines, called chemotherapy, are used to weaken or destroy the patient’s own bone marrow, stem cells, and infection-fighting system. The patient’s bone marrow then is replaced with blood-forming stem cells from a donor who doesn’t have sickle cell disease. The new bone marrow then produces red blood cells that are healthy since they do not contain a lot of haemoglobin S (3).

2] Stem Cell (Mesenchymal Stem cell-based) therapy in MDR/XDR TB:

MDR/ XDR TB is an increasing disease burden worldwide with a high prevalence in Eastern Europe, South Africa and South Asia (4, 17). MSCs have demonstrable properties of differentiating into three lineages of the germ layers, the endoderm, ectoderm and the mesoderm. They are hypo-immunogenic in nature and negative to HLA-DR. They are inert to co-stimulatory molecules in allogeneic applications, thereby proving to be a distinct cell candidate for immune modulation (4, 18, and 19). Mesenchymal stem cells constitutively express soluble immunomodulatory factors such as macrophage stimulating factor, PGE2, HGF and IL-10. Current reports have shown that tissue-specific MSCs can modify dendritic cell (DC) function demonstrated by an altered capacity to interact with T cells and induce tolerance or T cell unresponsiveness. The constitutive secretion of soluble immunomodulators by MSCs is an added advantage to counter single cytokine strategies for therapy such as anti-TNF-alpha, rhu IL-2, IFN-gamma etc. They address the local inflammatory milieu in totality; countering the anti-inflammatory cytokine secretions to balance the Th1/Th2 responses. Furthermore, it is speculated that the IL-10 released from MSCs, along with macrophage stimulatory factors, PGE2, and HGF would antagonize the IL-12 and TNF-alpha secreted by M.Tb (4).

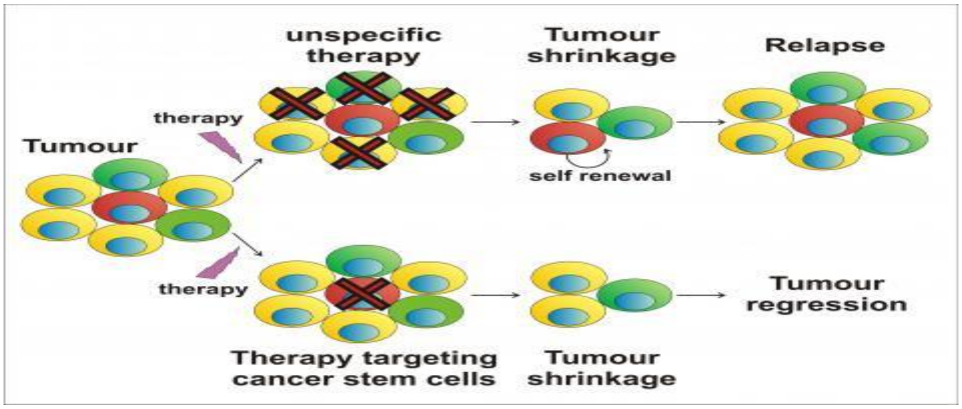
3] Stem cell treatment for HIV/AIDS:

Destruction of the immune system by the HIV is driven by the loss of CD4+T cells in the peripheral blood and lymphoid tissues. Viral entry into CD4+ cells is mediated by interaction with a cellular chemokine receptor, the most common of which are CCR5 and CXCR4.1 because subsequent viral replication requires cellular gene expression processes, activated CD4+ cells are the primary targets of productive HIV infection (5, 20). Recently scientists have been investigating an alternative approach to treating HIV-1/AIDS, based on the creation of disease-resistant immune system through transplantation of autologous, gene modified (HIV-1 resistant) hematopoietic stem and progenitor cells (GM-HSPC) (5,21,58).

4] Stem cell therapy to treat Cancer:

In the world, cancer remains a major cause of mortality. For over 30 years, stem cells have been used for the replenishment of blood and immune systems damaged by the cancer cells or during treatment of cancer with chemotherapy or radiotherapy. Apart from their use in the immuno-reconstitution, the stem cells have been reported to contribute in the tissue regeneration and as delivery vehicles in the cancer treatments. The recent concept of 'cancer stem cells' has directed scientific communities towards a different new wide area of research field and possible potential future treatment modalities for cancer. Despite recent advances in the treatments of cancer, the clinical outcome is yet far away from expectation. Use of stem cells in immuno-modulation or reconstitution is one of the methods used for decades in cancer therapy. Stem cells have self-renewal capacity with highly replicative potential in multi-lineage differentiation capacity (59). The current treatment regimens for cancer have shown limited survival benefits when used for most advanced stage cancers because these treatments primarily target tumor bulk not cancer stem cells (6,22,23, and 59).

Figure no:2 (61)



➢ **Cancer Stem cells**:

Cancer stem cells (CSCs) have been defined as cells within tumor that possess the capacity to self-renew and to cause the heterogeneous lineages of cancer cells that comprise the tumor. They have been identified in blood, breast, brain, colon, melanoma, etc. It is often considered to be associated with chemoresistance and radio-resistance that lead to the failure of traditional therapies (6, 24). Eradicating cancer stem cells, the root cancer origin and recurrence, has been thought as a promising approach to improve cancer survival or even to cure cancer patients. In recent years, several compounds were found have the ability to kill the cancer stem cells, such as salinomycin (25), curcumin, sulforaphane, a novel Gemini vit. D analogue and so on (6).

➢ **Mesenchymal stem cell- mediated gene therapy for cancer**:

Mesenchymal stem cells are multipotent stromal cells that differentiate into a variety of cell types. Some studies reported engineered MSCs specifically targeting multiple tumor types followed by local secretion of pigment epithelium-derived factor, therapeutic proteins (IFN Beta, IL-2), TNF-related apoptosis including ligand (TRAIL), expression of prodrug-activating suicide genes and delivery of replicating oncolytic viruses (6,26).

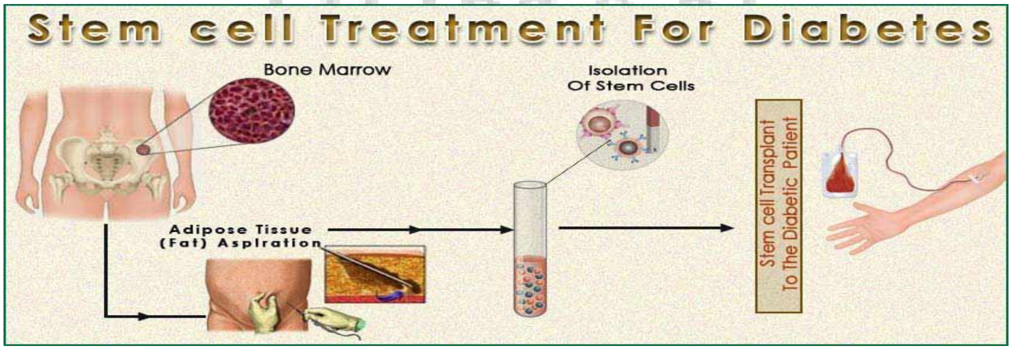
➢ **Differentiation therapy**:

Differentiation therapy is an approach to the treatment of advanced or aggressive malignancies so that they can resume the process of maturation and differentiation into mature cells. It aims to force the cancer cell to resume the process of maturation. Differentiation therapy may use either known differentiation-inducing agents and/or newly designed differentiation-inducing agents (6,7,27).

5] Stem cell therapy in Diabetes Mellitus:

Type 1 diabetes mellitus (T1DM) is a devastating chronic metabolic disease whose incidence has been rising at alarming rates during the last decade (8, 28). Diabetes is one of top 10 leading causes of morbidity and mortality, affecting nearly 350 million people worldwide. B-cell replacement represents an attractive prospect for diabetes therapy but treatment option remains quite limited (7). Exogenous insulin administration cannot mimic precise pancreatic beta-cell regulation of glucose homeostasis, thereby leading to severe long-term complications. Pancreas or islet transplant only provide partial exogenous insulin independence and induce several adverse effects, including increased morbidity and mortality. Mesenchymal stem cells (MSCs) have been envisioned as a promising tool for T1DM treatment over the past few years since they could differentiate into glucose-responsive insulin-producing cells. Their immunomodulatory and pro-angiogenic roles can be used to help arrest beta-cell destruction, preserve residual beta-cell mass, facilitate endogenous beta-cell regeneration and prevent disease recurrence (8). In recent experiments, scientists have been able to coax embryonic stem cell to turn into beta cells in the lab (5,29).

Figure no:3 (62)



- **Role of MSCs in therapy of Diabetes Mellitus:**

MSCs are hypo-immunogenic, allowing allogeneic transplant without histocompatibility or recipient conditioning being required (8). When MSCs are systemically administered they can selectively migrate and engraft in damaged tissue and differentiate into insulin-producing cells.

As immunomodulatory cells, MSCs can limit inflammation in damaged tissue, produce a broad range of trophic factors protecting parenchymal cells from dying by apoptosis and promote the proliferation and differentiation of endogenous precursors (8). Other sources for stem cells are: **1] Human Embryonic Stem Cells** and 2] **Islet beta cells** (7).

6] Stem cell treatment for Deafness:

Heller has reported success in re-growing cochlear hair cells with the use of embryonic stem cells (5,30).

7] Stem cell based treatment for infertility:

Culture of human embryonic stem cells (HESCs) in mitotically inactivated porcine ovarian fibroblasts (POF) causes differentiation into germ cells (precursor cells of oocytes and spermatozoa), as evidenced by gene expression analysis. HESCs have been stimulated to form Spermatozoon-like cells, yet still slightly damaged or malformed. It could potentially treat azoospermia. In 2012, oogonial stem cells were isolated from adult mouse and human ovaries and demonstrated to be capable of forming mature oocytes. These cells have the potential to treat infertility (5,31).

8] Stem cells therapy for Missing teeth:

In 2004, scientists at King's College London discovered a way to cultivate a complete tooth in mice and were able to grow bioengineered teeth stand-alone in the lab. Researchers are confident that the tooth regeneration technology can be used to grow live teeth in human patients. In theory, stem cells taken from the patient could be coaxed in the lab into turning into a tooth bud which, when implanted in the gums, will give rise to a new tooth, and would be expected to be grown in a time over three weeks. It will fuse with the jawbone and release chemicals that encourage nerves and blood vessels to connect with it. The process is similar to what happens when humans grow their original adult teeth. Many challenges remain, however, before stem cells could be a choice for the replacement of missing teeth in the future (5).

9] Stem Cell treatment For Heart Diseases:

According to the World Health Organization (WHO), cardiovascular diseases are the major cause of death globally, leading to estimated 17.3 million deaths in 2008 (9,32). Stem cell therapy for treatment of myocardial infarction usually makes use of autologous bone marrow stem cells (a specific type or all), however, other types of adult stem cells may be used, such as adipose-derived stem cells. Adult stem cell therapy for treating heart disease was commercially available in at least five continents as of 2007.

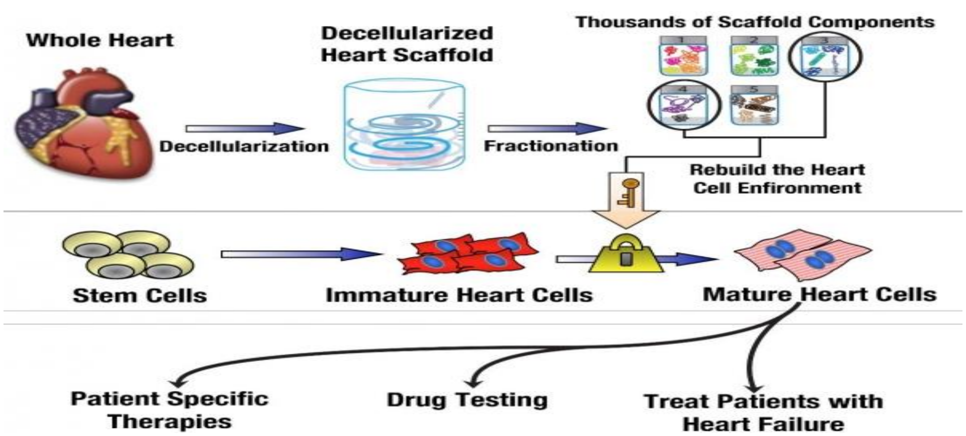
Possible mechanisms of recovery include (5, 1):

- ✓ Generation of heart muscle cells
- ✓ Stimulation of growth of new blood vessels to repopulate damaged heart tissue
- ✓ Secretion of growth factors
- ✓ Assistance via some other mechanism.

It may be possible to have adult bone marrow cells differentiate into heart muscle cells (5).

With increasing evidence, endogenous cardiac stem cells (CSCs) represent an attractive and promising cell candidate for cardiac repair and regeneration due to their autologous origin, cardiac-committed fate, and ability to develop into three major myocardial lineages. Recently, two phase 1 clinical studies, SCIPIO and CADUCEUS, using c-kit+ CSCS and cardiosphere-derived cells, respectively, confirmed early short-term safety and therapeutic efficacy in patients with ischemic heart failure (9, 33, 34).

Figure no: 4 (63)



Method of stem cell delivery:

1} Transvascular Route:

A transvascular approach is particularly well suited to treat the patients with acutely infarcted and reperfused myocardium. Stem cell can be infused directly into the coronary arteries and have a greater likelihood of remaining in the injured myocardium as a result of activation of adhesion molecules and chemokines (7).

2} Direct Injection into the Ventricular wall:

Direct injection of stem cell is used in patient presenting with established cardiac dysfunction in whom a transvascular approach may not be possible because of total occlusion or poor flow within the vessel of affected territory (7).

10] Stem cell treatment for Age-related macular degeneration:

Age-related macular degeneration (AMD) is one of the leading causes of irreversible blindness in people over 65 years in the world (10,35-38). Recent advances in the stem cell sciences have demonstrated that retinal pigment epithelium (RPE) cells can be generated from several types of stem cells (including embryonic stem cells, induced pluripotent stem cells, mesenchymal stem cells, etc) by cell co-culturing or defined factors. Additionally, studies also showed that visual function could be recovered by transplantation of these cells into subretinal space *in vivo*. Stem cells, particularly MSCs, have numerous biological effects, including secreting neurotrophins, promoting angiogenesis, regulating immune responses, antagonizing apoptosis, promoting extracellular matrix remodeling and activating adjacent host stem cells (10). MSCs are also an ideal carrier for introducing exogenous neurotrophic factors. These factors may also be expressed in the host retina and play biological effects. Therefore, MSCs are excellent candidates for treating dry AMD (10). The University Hospital of New Jersey reports that the success rate for growth of new cells from transplanted stem cells varies from 25% to 70%. In 2014, researchers demonstrated that stem cells collected as biopsies from donor human corneas can prevent scar formation without provoking a rejection response in mice with corneal damage (5).

❖ **Routes of transplantation:**

Routes that were tested for cell therapy for the retinal diseases are systemic administration intravenous, intravitreal injection and subretinal injection. Intravenous injection is much less invasive and easier to perform. Subretinal injection techniques: **1] injection of cell suspension, 2] injection of cell adhered to a matrix** (7).

11] Stem cell Transplantation for treatment of Autoimmune Disease:

Autoimmune Diseases (ADs) represent a heterogeneous group of disorders with genetic, environmental and individual etiological factors. The goals of treatments of ADs are to 1) reduce symptoms, 2) control the autoimmune process and 3) maintain the body's ability to fight disease. Allogeneic Hematopoietic stem cell (HSC) transplantation has been shown to be a relatively successful treatment for experimental ADs, and there are a number of reports of Bone Marrow Transplantation (BMT) being used to treat ADs in various mice (11,39-46). The diseases treated with the stem cell-based therapy are **1) Systemic Lupus Erythematosus (SLE**), which is a chronic auto-inflammatory disease of unknown etiology; **2) Multiple Sclerosis**, which affects the brain and CNS**, 3) Autoimmune Pancreatitis** and **4) Rheumatoid arthritis**, which primarily attacks the synovial joints (11).

12] Stem Cell therapy for Neurological Diseases:

I. Stem cell therapy for Spinal Cord Injury:

Spinal cord injury is one of the most prevalent disabling conditions in the world. It has an annual incidence of 15-40 cases per million (12,47). One of the important pathological processes in the white matter is a chronic and progressive demyelination of spared axons, which occurs primarily as a result of the delayed and widespread apoptosis of oligodendrocytes (13). Stem cell at different stages of maturation has been used for cellular transplantation. These cells have mainly included the neural stem cells, oligodendrocytes and their progenitor, mesenchymal stem cells, and bone marrow stem cells (12). Clinical and animal studies have been conducted into the use of stem cells in the cases of spinal cord injury (5).

Sources of stem cells for SCI:

✓ **Neural Stem Cells (NSCs):**

Neural stem cells are multipotent cells that are able to differentiate into neuronal and non-neuronal cells, and thus, can replace multiple lost elements at the site of SCI. The sources of human NSCs are divided into embryonic and adult depending on the development level at the time of isolation (12).

✓ **Mesenchymal stem cells (MSCs):**

These cells have the capacity to increase tissue preservation and decrease cyst and injury size (12). They are also capable of producing various neurotrophic factors that promote neuronal survival and functional recovery. These represent an attractive source for cellular transplantation (12, 48).

✓ **Bone marrow stem cells:**

II. Stem cell treatment for Parkinson's disease:

First described in 1817, PD, the second most common neurodegenerative disease (49), is a neurological degenerative disease that results in the loss of dopaminergic neurons within the substantia nigra (14,50,51), leading to a loss of motor function (14). Although the etiology of idiopathic PD is not known, several predisposing factors for dopaminergic depletion associated with the disease have been suggested, including programmed cell death, viral infection, and environmental toxins (13). The current drug treatment for PD supplies the surviving dopamine neurons with L-DOPA, which they convert to dopamine (14,52).

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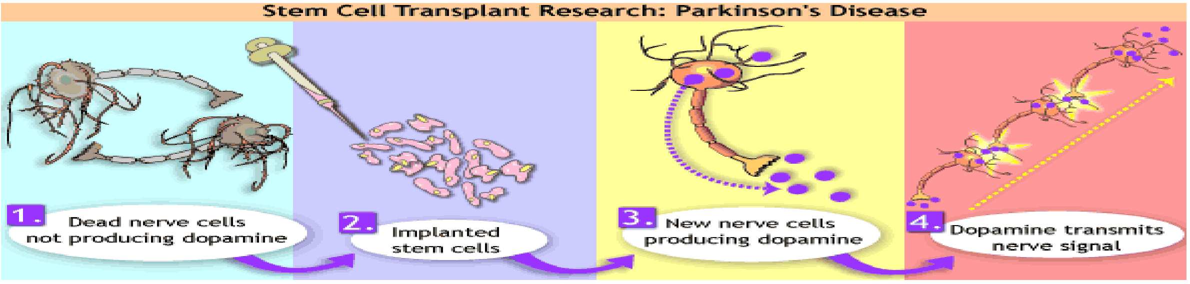

Sources of stem cells to treat PD:

- ✓ **Mesenchymal stem cells**: They have been proposed as potential treatment for PD. MSCs significantly preserved the number of dopaminergic neurons and tyrosine hydrolase-positive cells *in vitro* and *in vivo* (14,53).
- ✓ **Neural Stem Cells**: Transplantation of NSCs in the brain attenuates anatomic or functional deficits associated with injury or disease in the CNS via cell replacement, release of specific neurotransmitters, and production of neurotrophic factors that protect injured neurons and promote neuronal growth (13).
- ✓ **Embryonic Stem Cells**: These also having the potential to treat PD via cell differentiation but they are also having the risk of formation of tumors (7).

III. Stem cell treatment for Alzheimer disease (AD):

As one of the most common causes of dementia, AD affects 5.3 million Americans (14,54). AD is characterized by degeneration and loss of neurons and synapses throughout the brain, particularly in the basal forebrain, amygdala, hippocampus, and cortical regions. Memory and cognitive functions of patients progressively decline (13). Currently available drugs for the treatment of AD are purely for symptoms and among these drugs are the cholinesterase inhibitors (14,55-57). As for the pathogenesis of AD, the amyloid cascade hypothesis postulates that memory deficits are caused by increased levels of both soluble and insoluble Aβ peptides, which are derived from the larger amyloid precursors protein (APP) sequential proteolytic processing (13). NSCs have the potential to treat the AD. NSCs may also be useful to augment growth factors. NSCs are also reported to express neurotrophic factors and promote axonal growth in SCI (14).

IV. Other diseases treated with Stem cell transplantation are: 1] Amyotrophic lateral sclerosis, 2] Huntington's disease, 3] Stroke, 4] Brain Tumor, 5] Lysosomal Storage Disease (13).

13] Stem cell therapy for Disaster Injuries:

- Haematopoietic disorders
- Acute radiation syndrome

- Musculoskeletal injuries
- Burns and skin injuries
- Liver Damage
- Kidney Damage (15).

CONCLUSION

By referencing the sources mentioned below and reviewing papers, we come to across to the fact that stem cell-based therapies are important in the disease management. Till today, many reviews on stem cell therapy were published. There is much controversy regarding the treatment of stem cell-based treatments. Stem cell therapy, particularly employing MSCs, holds tremendous potential to stimulate or accelerate reparative processes and provides sufficient graftable cells. The use of stem cells is limitless because of their ability to renew, differentiate themselves into any other type of cell. Thus, we discuss a review on stem cell-based therapy for various diseases like cancer, Diabetes, Age-related macular degeneration, PD, etc.

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