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# Stem Cell Therapy and Regenerative Medicine

*Introduction*

Regenerative medicine, also referred to as stem cell therapy, is a discipline of medicine which aims to replace or repair either diseased or damaged cells or tissues in the human body with the aim to restore normal body functions (MRC, np). Regenerative medicine is considered key to future patient care. Many health organizations and governments have invested heavily in regenerative medicine.

Patients' needs are increasing each day. Each day comes with a new challenge to the field of medicine. This challenge can be attributed to an increase in the aging population. It is therefore important for those working in the medical research field to find new ways to meet these increasing demands. Great progress has been made in regenerative medicine field. Regenerative medicine provides very effective means of treating both organs and tissues that could not be treated previously. Regenerative medicine has come up and is still coming up with new ways of treating and managing chronic diseases like heart failure, diabetes and degenerative joint, bone and nerve conditions.

Regenerative medicine aims to come up with ways of healing injuries and diseases that were previously considered untreatable or permanently damaged. Research in regenerative medicine wants to avail such methods of treatments for clinical use. Treatment with regenerative medicine includes both in vitro and in vivo procedures. In vitro treatment involves treating the body through therapy implantation studied in the laboratory. On the other hand, in vivo treatment involves treating the body through trials and studies conducted inside a living body; with the aim of stimulating self- healing of organs that were previously considered irreparable.

Regenerative therapy scientists are utilizing principles of material science, bioengineering, and cell transplantation to come up with a biological replacement that can help restore and maintain the normal functioning of either diseased or damaged body organs or tissues. The rapid advancement greatly aids reconstruction of biological tissue or organ tissue in the medical arena. Injection is one of the techniques used here; by introducing functional cells to a site of an organ or tissue that is non- functional. This introduction aims to stimulate regeneration of the tissue or organ, to aid in the production of growth factors or hormones or to promote vascularization.

The field of regenerative medicine is mainly concerned with four main areas. These areas include; medical devices and artificial organs, tissue engineering and biomaterials, cellular therapies and clinical translation (McGowan Institute, np). Regenerative medicine has made it possible to artificially grow organs in the laboratory then place the organ in a human. Scientists, through powerful technology, are now able to create new parts of the body from a patient's

tissues and cells. This innovation will also help reduce cases of tissue rejection during transplant since the tissues and cells are now from the same body. Scientists are also able to replace either diseased or damaged tissue or organs with cellular components, commonly referred to as biohybrid organs, or replaced synthetic devices, also commonly referred to as fully artificial organs (McGowan Institute, np).

There are various regenerative medicine strategies. They include; stimulation of the repair processes of the body, transplantation of either progenitor cells or tissues or stem cells and using cells to deliver therapeutic agents which include cytokines and genes. All these strategies aim to guide, harness or stimulate repair processes of the body.

The three main approaches in regenerative medicine are rejuvenation, replacement, and regeneration (Mayo Clinic, np). Rejuvenation involves boosting the heal capabilities of the body. Some of the body parts do self- heal like others. For example, when the skin is cut it can repair and self- heal after a few days. Cells in other organs of the body such as the heart and lungs were thought not to be able to self-heal. These cells were thought to be terminally differentiated; unable to undergo further division. However, through advancement in regenerative medicine, it has been discovered that these cells can remodel themselves and have some capability of self-healing. Advanced research is being undertaken to enhance the self- healing of such cells. The second approach is through replacement. In this approach, organs, tissues or cells from a donor, either deceased or living, are replaced with already damaged organs, tissues or cells. Replacement is common in organ transplants such as the kidney, liver and heart transplants. More research in this approach is done to reduce cases of organ rejection, overcoming donor shortage and also overcoming the necessity for immunosuppression. Regeneration, on the other hand, involves carrying certain types of cell products or cells themselves to diseased organs or tissues. The aim of these delivered cells and cells products is to restore the normal functioning of the organ or tissue where they have been delivered. An example of regeneration is a bone marrow transplant. Regeneration can be achieved through cell products such as growth factors or cell-based therapy. This approach works from within the body hence it is definitive and provides a solution for various health issues.

The most important components of regenerative medicine are the cells and biomaterials (Atala, np). Biomaterials can either be synthetic or natural matrices. Synthetic matrices are commonly referred to as scaffolds and form an important tool in regenerative medicine. Biomaterials can be used to introduce bioactive factors into the damaged or diseased organs or tissues. Biomaterials can also attract growth factors and hormones from the body after implantation. Another function of biomaterials is to create a conducive environment for restoration of tissue functions and structure. Biomaterials also guide the tissue's growth direction. In certain conditions, biomaterials are introduced without cells. Such a process aims to stimulate the body's repairing ability.

Research in various areas of medicine has enabled the advancement of regenerative medicine. The most important area of research is the stem cell. Other areas of research include; gene therapy, tissue engineering, cellular therapeutics, chemical biology, cell biology development, biomaterials, and nanotechnology. In most cases, regenerative therapy begins with the collection of a particular type of cell from the patient, for example, the skin cells. The patient's cells are then reprogrammed in a laboratory to add certain characteristics to the cells. The reprogrammed cells are then introduced back into the patient's body to treat the disease.

Stem cells are critical for regenerative medicine. These cells provide various opportunities for clinical applications due to their unique qualities. Through the differentiation process, stem cells develop into different types of cells; for example lung cells, skin cells and brain cells. Research on stem cells is being done on various categories of stem cells including the embryonic and adult stem cells. A variety of progenitor cells are also being studied. Such cells include cells found in the umbilical cord blood and pluripotent stem cells which are bioengineered cells. Each stem cell has its unique quality and versatility (Mayo Clinic, np).

The body uses stem cells to heal itself. Regenerative medicine is exploring the opportunity to use stem cells to repair tissues destroyed through wear and tear, trauma and diseases. It has been found out that the umbilical cord, usually gotten rid of at birth, contains numerous stem cells. The umbilical cord can be stored, so that one has a supply of his/her cells in case one ever needs cell transfer. The latter solves the problem of few compatible donors and also reduces cases of body rejection of foreign cells.

The rapid development in the field of stem cells has opened new avenues for regenerative medicine. Considering venues such as cellular programming and therapeutic cloning will in future provide an unlimited source of cells which can be used in engineering applications. Although a lot of research is still being done on stem cells, some of its applications are already being successfully applied in a clinical setting.

Each day diseases are becoming more destructive that through traditional medicine, the only way to cure such diseases is by replacing the whole organs or tissues affected. However, research on regenerative medicine aims to change this. The work of regenerative medicine aims that in future there is no need to replace entire organs. For instance, heart disease cases are on the rise in the United States (McGowan Institute, np). Currently, medicine only offers a heart transplant as the solution. Considering there is a shortage of donors and cases of rejection, this is very problematic for the field of medicine. Heart valves are normally affected by heart diseases. Through regenerative medicine, scientists have been able to create heart valves from human cells. Using biomaterials, it will be easier to treat heart diseases; heart valves for transplant will be from the patient's cells.

Through clinical translations, promising therapies are tried. Milestones have been made in the regenerative medicine field. It is therefore important to try these new forms of treatment to determine whether they can be used in clinical practice. The United States is spending more and more each year in its healthcare system. In 2015, the amount spent on health was $3.2 trillion, representing 17.8% of the country's Gross Domestic Product. This figure was also a 5.8% increase from the previous year. More than 610 000 lives are lost annually in the United States due to heart complications making heart diseases a leading cause of death. The government also spends about $207 billion every year on heart diseases. Another chronic disease that can be cured by regenerative medicine is diabetes. Over 29 million people are living with diabetes in the United States, with another 86 million living with prediabetes, increasing their chances of contracting diabetes or other chronic diseases. Another disease is the Valvular Heart Disease, commonly referred to as VHD. VHD claims 20000 lives each year with another 90000 hospitalized, costing the United States $9 billion (McGowan Institute, np). VHD mostly occurs among the aging population. All these conditions can be cured through regenerative medicine. A lot less will be spent on treating such diseases. It is clear that regenerative medicine is a timely development and it will save many lives and also save the country a lot of money.

*Stem cells sources*

Stem cells are categorized into two; embryonic stem cells (ESC) and non- embryonic stem cells (non- ESC). ESC has the ability to undergo cell differentiation forming three germ layers hence are referred to as pluripotent. The layers formed are mesoderm, endoderm, and ectoderm. On the other hand, non- ESC are multipotent meaning their differentiation is limited towards few lineages. The ability of these cells to isolate and expand and their potency are essential properties for the development of regenerative medicine. The focus of current research is on the niche or the microenvironment of the stem cells (Bajada et al., pp. 3). The niche of the stem cells includes; intercellular contact, signaling molecules and the interaction between the neighboring extracellular matrix of the stem cells and the cells. The microenvironment of the stem cells is considered to control the property of the cell that enables it to self- renew (Bajada et al., pp. 3). Further research is being done to determine what controls the differentiation of stem cells. Stem cells differentiate according to the host niche. The cells have the ability to adapt to the environment they are implanted producing the demanded cells and organs. When bone marrow cells were implanted into a neutral environment, the cells formed neuronal cells (Bajada et al., pp. 3).

Embryonic stem cells are sourced from the inner cell mass of a blastocyst aged 5-6 day (Bajada et al., pp. 5). To create an ESC line, the inner cell mass is cultured on feeder layers made up of human feeder cells or mouse embryonic fibroblasts. However, recent research has shown that a feeder layer is not necessary for the growth of embryonic stem cells (Bajada et al., pp. 5). There are ethical issues surrounding the source of blastocysts for ESCs. Legislation pertaining embryonic research differs in various countries. Nuclear cloning is mostly used a blastocyst source (Bajada et al., pp. 6). There are two types of nuclear cloning; therapeutic cloning and controversial reproductive cloning. In controversial reproductive cloning, it is possible to generate an infant with the same genetic makeup as the donor cell. In therapeutic cloning, it is possible to generate embryos at their early stages which are explanted to form ESC lines which have same genetic makeup as the donor cells (Bajada et al., pp. 8). Stem cells from this source have the unlimited ability to differentiate.

Non- ESC is not as superior as ESC. They have limited pluripotent ability (Bajada et al., pp. 8). Non- ESC, throughout their lifetime, show potential for multipotency differentiation. There are different sources for non- embryonic stem cells. Some are obtained from the amniotic fluid. Multipotent stem cells can be separated from the amniotic fluid. These cells show certain characteristics same to ESC (Bajada et al., pp. 8). Stem cells from the amniotic fluid represent an intermediate phase between ESC and other non- ESCs. Cells obtained from amniotic fluid are able to grow without a feeder layer; every 36 hours they were observed to double (Bajada et al., pp. 8). Based on the germ layers, the cells were able to differentiate into functional cells. The cells also formed neuronal, myogenic, endothelial, adipogenic, hepatic and osteogenic cells (Bajada et al., pp. 8). The sources for such cells are easily and widely available; this is a major boost for regenerative medicine.

Another source for non- ESCs is the umbilical cord. Due to its closeness to the embryo, it is thought that it has some of the pluripotent characteristics associated with ESCs (Bajada et al., pp. 8). Stem cells can be obtained from the cord lining and from the cord blood. The umbilical cord is normally discarded, hence provides a limitless supply. There are no ethical issues surrounding this source and it can always be banked for future use.

Non- ESC can also be obtained from the bone marrow; this is a more common source and is already being used in clinics. Stem cells obtained from the bone marrow are knowns as adult stem cells. The bone marrow is formed by fibroblast-like cells which form a network. The adipose stromal cells have a subpopulation of multipotent cells among them (Bajada et al., pp. 9). The cells are known as mesenchymal stem cells (MSCs). Research indicates that these cells can also differentiate into various functional cells (Bajada et al., pp. 9).

Another source for non- ESC is through in vitro MSC differentiation. Human MSCs are separated from the bone marrow's mononuclear layer. Ten percent fetal calf serum is used to culture the mononuclear cells and they cells then divide rapidly (Bajada et al., pp. 9). Various methods can be used to differentiate MSCs into adipocytes, chondrocytes, tenocytes, and myocytes.

Another common source for non- ESC is the adipose tissue. This is already being applied in clinics. Multipotent cells can be obtained from the adipose tissue and they can be differentiated 'in vitro' to form various cell lines such as chondrogenic, neurogenic and osteogenic lineages (Bajada et al., pp. 11). Cardiomyocytes and myocytes can also be obtained from stem cells derived from the adipose tissue. This source has the advantage of being abundant and has numerous cells hence easy to harvest.

Monocytes can also act as a source for non- ESC. Through research, it has been found that blood monocytes can dedifferentiate under certain culture conditions. They form different cells such as islet-like cells, endothelial, fat cells and epithelial cells (Bajada et al., pp. 13). This makes monocytes important to regenerative medicine. Non- ESCs can also be obtained from endothelial cells and vascularization (Bajada et al., pp. 3).

*Contraindications for stem cell therapy*

Patients should provide written consent in order to undergo stem cell therapy. The therapy is conducted according to the Good Manufacturing Practice. It is inadvisable for patients with the following conditions to undergo stem cell therapy (Advancecells, np);

- Patients who have had surgery six weeks before beginning undergoing stem cell therapy.
- Patients who have congenital blood disorders.
- Patients with hemoglobin amounting to 10 or less.
- Patients with severe malnourishment and cachexia.
- Patients who are either pregnant or breastfeeding.
- Patients with positive serology for diseases considered infectious.
- Patients whose immunity has been compromised.
- Procedure for implanting stem cells

Candidates for the implantation procedure first consult with certified surgeons to review their medical history. A physical examination is also conducted to monitor vital signs of the patients. Part of the examination may include MRI and X-ray.

For the implantation phase of the procedure, the patient is given anesthesia through an IV, same as in a colonoscopy procedure. The patient may be awake or talking during the procedure, however, he/she will remember little of the procedure. An orthopedic surgeon, experienced spine surgeon or trained physician removes some of the source for the stem cells, either the adipose tissue or bone marrow.

When using the adipose tissue as the harvesting site, the procedure is considered short and harmless. It is less invasive and much easier compared to harvesting from the bone marrow (Startstemcells, np). The adipose tissue has a higher amount of mesenchymal stem cells compared to the bone marrow.

In a treatment procedure where the adipose tissue is being used, fat in small amounts is extracted from the patient's waist area. This process is referred to as liposuction (Startstemcells, np). The stem cells are then obtained through separation from the other cells of the source site. A centrifuge machine is used to separate the stem cells from the fat cells. The separated stem cells are then enriched with the patient's blood plasma. The cells are then photoactivated using an AdiLight machine (Startstemcells, np). The cells undergo further preparation before being reintroduced into the patient's body. It can be injected into the injured or damaged areas to help the body in healing. The stem cells are placed directly close to the damaged or injured tissue (ProgenCell SCT, np). This increases the chances of tissue recovery. The cells could also be introduced into the patient's body through a standard IV drip. Here, the activated stem cells are placed into a saline drip bag (Startstemcells, np). Using both intravenous deliveries through IV drip and direct injection of cells are recommended (Okyanos Center, np). Combining the two addresses issues which cause restricted blood flow, inflammation, and destructive immune response.

For a bone marrow extraction, the doctor disinfects the bone marrow extraction area then using an injection offers anesthetic. The harvesting process takes about 15-20 minutes (ProgenCell SCT, np). According to the target stem cell required, the doctor takes a minimum amount bone marrow. However, depending on the amount of tissue to be regenerated, the doctor obtains another small amount of injections in other parts of the body (ProgenCell SCT, np).

However, in some cases the stem cells are first stored; they are not reintroduced into the patient's body after a few minutes (Cancer Org., np). A medicinal procedure is carried on a patient before receiving frozen stem cells. The drugs reduce chances of the patient's body from reacting to the preservative used to store the stem cells (Cancer Org., np). The frozen stem cells are first thawed then reintroduced into the patient's body right away. The time for this process depends on the amount of fluid the stem cells were stored in (Cancer Org., np).

*Healing process after stem cell implantation*

Healing from stem cell implantation is a complex process. It involves body mechanisms at cellular and molecular levels. The stem cells circulate the body for a while before being attracted by the intended protein secreting organ. After reaching the damaged tissue, the stem cells begin to form new tissue.

During the first 3-5 days after implantation of stem cells, the patient feels bruised in the area where the stem cell harvesting took place (ProgenCell SCT, np). The patient can tolerate this discomfort and he/she can use painkillers. Patients are monitored to make sure that the liposuction incisions and procedure sites are healing properly.

If the patient's stem cells were first stored before reintroduction into the body, there may be several effects (Cancer Org., np). But the side effects are mild and rare. The side effects are caused by the preserving agent during storage of the stem cells (Cancer Org., np). This agent is known as dimethylsulfoxide. The patient has a strong taste of creamed corn or garlic in their mouth. The patient's body also smells of the same (Cancer Org., np). This lasts a few days. Other side effects include; shortness of breath, chest pain, low blood pressure, low urine output, fever, fatigue, and coughing (Cancer Org., np). During recovery, the patient experiences an emotional roller coaster, with feelings such as anxiety, joy, distress, depression, and anger very common (Cancer Org., np). It is therefore important for the patient to have support from friends and family.

During the recovery process, first, the cells have to engraft then start multiplying and forming new blood cells. After 2-6 weeks of the implantation of the stem cells, the blood count is expected to return to safe levels (Cancer Org., np). However, this depends on the type of implantation and the patient. During the first weeks, the patient has a low number of platelets, red and white blood cells (Cancer Org., np). The doctor administers antibiotics to prevent the patient from contracting infections. This continues until the count of white blood cells reaches a certain level. Patients may still contract infections due to a low number of white blood cells, a condition referred to as neutropenia. Some may experience bleeding due to few platelets, a condition referred to as thrombocytopenia. In some cases, transfusion of platelets and red blood cells is done until the bone marrow begins forming new cells (Cancer Org., np).

*Improving outcome of stem cell therapy*

There are new ways of improving the results of stem cell therapy. Certain diseases and conditions may lead to an impaired immune system, metabolism disorders and increase in production of free radicals. Stem cells are undifferentiated cells hence they contain special capabilities for health recovery. It is therefore important to detoxify the body so that the stem cells implanted into the body have a higher chance of regeneration. Detoxifying the body increases the hardiness and volume of the stem cells (Startstemcells, np). Pharmacological agents

used by standard medical practice hinder the body's natural ability for regeneration and self-defense (Startstemcells, np). There are new innovative ways of reducing such hindrance.

Laser blood stimulation can be used to improve the results of stem cell therapy (Startstemcells, np). According to numerous studies, laser light has a huge influence on white blood cells including lowering blood cholesterol, increasing blood's viscosity, antibodies, interleukins and interferon growth factors, and antiviral and antiviral effect (Startstemcells, np). Laser blood stimulation also helps in improving the flow of nutrients, strengthening of the immune system and increasing the blood flow (Startstemcells, np). All these improve the body's resistance to diseases hence improving the stability and number of stem cells. This leads to resilient and active stem cells which could be harvested and activated in later processes.

Oxygenation is also another way of improving results of stem cell therapy (Startstemcells, np). All cells including stem cells require oxygen to survive. Certain diseases create extreme conditions for body metabolism on a cellular level. Oxygenation improves the body's immune system, has dilation effect on blood vessels and also anti-inflammatory effect. Oxygenation also improves blood flow throughout the body (Startstemcells, np). Improved blood flow in the capillaries increases the number of resilient and stable stem cells in the body (Startstemcells, np). This increases the survival chances of the cells during harvesting and activation.

Physiotherapy is also another way of improving results of the stem cell therapy (Startstemcells, np). During the preparatory phase of the stem cell therapy, it is important to reduce certain symptoms. These include; reducing inflammatory processes, increasing tissue and organ capacity, treating spasm and increasing muscle coordination and strength. Physiotherapy also helps in improving respiratory and cardiovascular capacity. All these improve the efficiency of stem cell therapy (Startstemcells, np).

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