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A Review on Stem Cellstherapyis A New Era in Type 2 Diabetes

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ABSTRACT

Diabetes is one of the most leading cause of death worldwide. Around 40 million diabetics are reported in India. Stem cell therapy is a branch of medicine that involves introducing stem cells into a diseased tissue which triggers the body's ability to heal itself. Stem cell therapy is a latest technique which can be used to treat diabetes mellitus. In India the success rate of stem cell therapy in diabetes mellitus is approximately 70 - 80 %. As this stem cells may be harvested from the bone marrow, umbilical cord and matured adult. In the present review we are discussing about the use of stem cell therapy in type 2 diabetes and how it works. Type 2 diabetes mellitus results from combination of insulin resistance and dysfunction of insulin producing beta cells which cannot be reversed by existing therapeutic strategies, transplantation of stem cells which are differentiating into insulin producing cells is one of the most promising strategy for treating type 2 diabetes.

Key words:
Blood Cancers, Mesenchymal Stem Cells, Stem cell therapy, Totipotent, Type 2 Diabetes.

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INTRODUCTION

A stem cell has the remarkable capability to expand into specialized cell types in the body. In the future they may be used to restore new cells and tissues that have been lost or damaged due to disease. Human body is made up of different cells, most of the cells have specialized functions to perform, and provide new cells for the body as it grows. They have two unique properties, they can rapid self-renewal (divide over and over again to produce new cells) [1]. In some parts of the body, such as the gut and bone marrow, stem cells regularly divide to produce new body tissues for maintenance and repair[2]. As they divide, they can transformation into the other categories of cell that make up the body (differentiate into a specific adult cell type **figure 1**) [1,2].

CLASSIFICATION BASED ON POTENCY

Potency is a term used to indicate ability of the cell to differentiate into multiple specialized cell types. Cultured stem cells are grouped according to their potency,

- **TOTIPOTENT**: These stem cells have ability to form entire organism which are isolated from fertilized egg which means zygote
- **PLURIPOTENT**: These stem cells have an ability to form almost all of body cells lineages which include endoderm, mesoderm, ectoderm.
- **MULTIPOTENT**: These stem cells have an ability to form multiple cell lineages but not able to form all the body lineages
- **OLIGOPOTENT**: theses stem cells have an ability to produce more than one cell lineage for example: myeloid progenitor cells. Which leads to different cell types but lack cell renewing capacity,
- **UNIPOTENT**: These stem cells have an ability to produce only single cell lineage for example: spermatogonia stem cells [3].

There are 4 major distinguished types of stem cells, that are Embryonic stem cells, Adult stem cells, Induced pluripotent stem cells, Mesenchymal stem cells.

EMBRYONIC STEM CELLS (ESC)

Embryonic stem cells are obtained from the inner cell mass of blastocyst which is formed after three to five days after an egg cell is fertilized by a sperm. The cells present inside the inner cell mass will give rise to more specialized cells that give rise to entire body of all tissues and organs. Embryonic stem cells are pluripotent meaning which gives rise to every cell type in full formed body. They provide renewable resource for studying normal development and disease and for testing drugs and also for therapies.

TISSUE SPECIFIC STEM CELLS [ADULT STEM CELLS]

These are also known as somatic stem cells that are more specialized than embryonic stem cells and had an ability to differentiate into different cell types for the specific tissue or organ. For example: Hematopoietic stem cells in the bone marrow can differentiate into red blood cells, white blood cells and platelets. But they don't differentiate into lung or liver or brain cells. Some tissues and organs contain small group of tissues specific stem cells which replace cells when they are lost in normal day to day living or in injury such as in skin and blood.

MESENCHYMAL STEM CELLS (MSC)

Mesenchymal stem cells are the stem cells isolated from, stroma, the connective tissue that surrounds other tissues and

organs. The mesenchymal stem cells are found in the bone marrow and capable to form bone, cartilage, fat cells. They present immune modulatory property and being tested for treatment of many disorders and their characteristics depends on where they originate in the body and how they are isolated and grown.

INDUCED PLURIPOTENT STEM CELLS (IPSE)

Induced pluripotent stem cells that are engineered in the lab by converting tissue specific cells. They are useful for learn about normal development and disease onset and progression and also useful for developing and testing new drugs and therapies. They have many same characteristics of embryonic stem cells it means they gave rise to all cell types in the body but not exactly. Researches are experimenting with many alternative ways to produce induced pluripotent stem cells which are ultimately used as source of cells in medical treatment [4].

Stem cell therapy

Stem cells can be collected from the umbilical cord of a baby birth and adults bone marrow. Stem cell therapy is a treatment of various disorders, it may be non-serious or life threatening by using cord stem cells. The cells can be frozen in cell banks and used to treat *more* than 80 disorders some of the diseases are listed in table 1. The common degenerative disorder includes diabetes mellitus, osteoarthritis, stroke, chronic renal failure, congestive cardiac failure, myocardial infarction, Alzheimer's disease etc. The treatment is safe, speed, and completed within one or two days.

Table I List of diseases treated with stem cells[5]

Blood cancers	**Other Inherited Immune System Disorders**
Leukemia	**Metabolic Disorders**
Myeloproliferative Neoplasms	Leukodystrophy Disorders
Myelodysplastic Syndromes	Lysosomal Storage Diseases
Multiple Myeloma	Mucopolysaccharidosis (MPS) Storage Diseases
Solid Tumors	Diabetes, Type 1
Non Malignant Blood Disorders	Diabetes, Type 2
Anemias	**Other like**
Hereditary Bone Marrow Failure Syndromes	Acute Myocardial Infarction
Inherited Red Cell Abnormalities	Respiratory Distress Syndrome (ARDS)
Inherited Platelet Abnormalities	Aging Frailty
Immune Disorders	Alopecia
Severe Combined Immune Deficiency (SCID)	Alzheimer's Disease
Neutropenia's	Amyotrophic Lateral Sclerosis
Phagocyte Disorders	Ankylosing Spondylitis
Inherited Disorders of the Immune System & other Organs	Autism

STEM CELL THERAPY IN TYPE II DIABETES MELLITUS

Diabetes mellitus is a group of chronic diseases characterized by elevated blood glucose levels due to different causes with abnormal β-cell biology playing a pivotal role. Over recent decades, the population affected by diabetes has been increasing in both developed and developing countries. The International Diabetes Federation (IDF) recently estimated that 425 million people are affected by diabetes worldwide [6]. The estimate of the actual number of diabetics in India is around 40 million. This means that India actually has the highest number of diabetics of any one country in the entire world. Amongst them, 80% live in low- and middle-income nations [7], and a large proportion reside in the Asia–Pacific region. In a Chinese nationwide survey carried out in 2013, 11.6% of adults aged >18 years had diabetes; that is, one in nine Chinese adults were affected [8].

Diabetes increases the risk of premature mortality and morbidity as a result of multisystem complications during the lifelong disease course [9]. These include atherosclerotic cardiovascular diseases, renal failure, visual loss, foot ulcer and amputation, all of which are highly preventable and treatable. It has been estimated that 68% of adults with diabetes aged >65 years died of some form of coronary heart disease (CHD), whereas 16% died of stroke [10]. Additionally, diabetes is associated with morbidities, such as cancer, depression, and physical and mental disabilities [11].

Type 2 diabetes mellitus is characterized by relative insulin deficiency and insulin resistance, in stem cell therapy, transplantation of insulin producing cells (IPC) is an important procedure for treating diabetes mellitus. Mesenchymal stem cells (MSC) are more preferable stem cells and they are considered an ideal candidate cell type for treatment of DM.

MSCs are known to promote the regeneration of pancreatic islet beta cells, protect endogenous pancreatic islet beta cells from apoptosis, and ameliorate insulin resistance of peripheral tissues by providing a supportive niche microenvironment. MSC-related research has demonstrated exciting therapeutic effects in glycemic control both in vivo and in vitro, and these results now have been translated into clinical practice. These transplanted stem cells make better peripheral insulin resistance and promote better beta cell regeneration. Translation of islets cells from donors was first performed in 1999 these Results in increased insulin production, normal blood glucose levels, normal glycosylated hemoglobin levels (HbA1c), and decreased requirement of insulin. The drawbacks of these therapy include less availability of donor's, complications of immunosuppressive agents and warn out of the transplanted cells [12].

MECHANISM OF STEM CELL THERAPY

The primary mechanism of stem cells are differentiation of mesenchymal stem cells into insulin producing cells. These differentiation of endocrine compartment of pancreas was regulated by some main transcription factors such as Pdx-1, Ngn-3, NeuroD1, Pax4, and Pax6. These cells activate the pathway which is responsible for inducing differentiation of MSCs into IPSC. In addition to that, MSCs also promote the regeneration of endogenous pancreatic islet beta cells by migrating to the injured islet cells. The MSCs participate in the repair processes by secreting a variety of cytokines and growth factors that have both paracrine and autocrine activities and

also had immunoregulatory capacity because of the low intracellular expression of class II major histocompatibility (MHC) proteins and co-stimulatory molecules [13].

PROCEDURE

A process called apheresis is used to obtain stem cells for transplantation. Before 2-4 days of apheresis, the donor was given a medication to increase the number of stem cells which is released into blood stream and these bloods is taken through large vein in the arm or by central venous catheter. These blood goes to the machine (Figure 2) which separate the stem cells from the blood which are useful and the remained blood was returned to the donor and these stem cells are processed and stored. This process takes up to 4-6 hours. The stem cells are then isolated, processed combined with platelet rich PRP and growth factors and then injected back into the recipient to complete the stem cell diabetes treatment. These stem cells then differentiate into pancreatic islet-like cells, demonstrating many of the expected characteristics of true pancreatic islet cells including the ability to secrete insulin, glucagon and somatostatin and they are able to synthesize and secrete insulin in a glucose responsive manner [14].

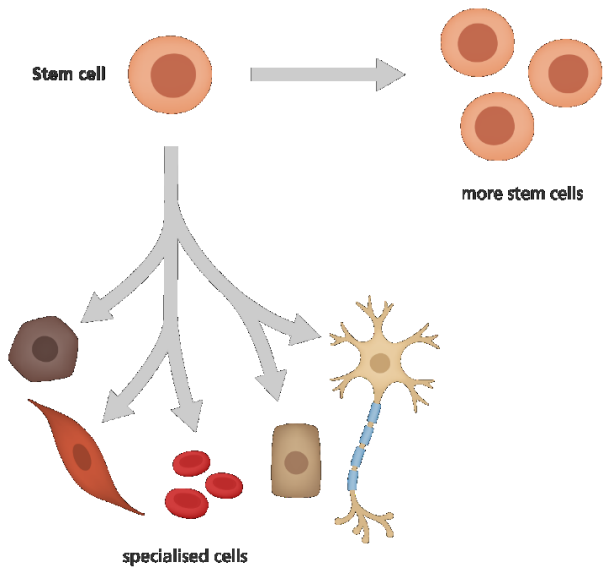

Fig 1: Stem cell giving rise to more stem cells or specialized cells

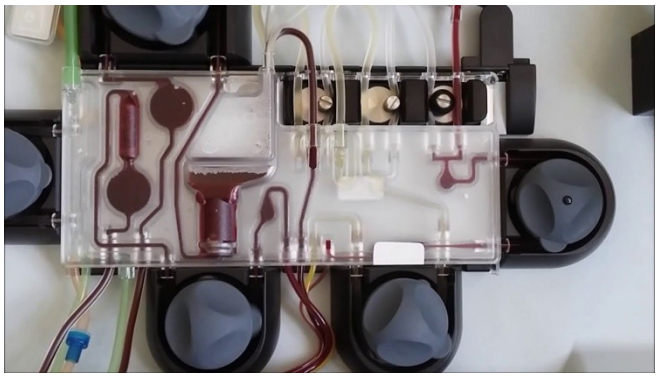

Figure 2 Apheresis Machine [15]

HOW THEY WORK

Stem cells have three different properties which lead to proper curation of disorders by

PLASTICITY

The stem cells have a characteristic of plasticity seen in multipurpose stem cells which mean capacity to produce cells outside the lineage constriction called in term of trans differentiation.

HOMING

Stem cell homing is an approach, whereby Stem cells react to inclinations of chemo attractants by moving up these angles and cabin inside definite tissue zones. They have the capacity to get pulled into the site of damage.

Engraftment

Stem cell engraftment is an approach, wherein transplanted stem cells go through the blood deep into bone marrow, where they start to make new white blood cells, red blood cells, and platelets. It as a rule occurs inside 2 to 4 weeks after a stem cell transplant. They join with new tissue to coordinate with the parent tissue easily [16].

DELIVERY OF STEM CELLS

The delivery of stem cells is normally done by injecting the stem cells into the pancreatic artery via catheter. Patient who are unable to take catheterization process may choose to receive the stem cell diabetes treatment intravenously which include stem cells are injected in to the physiological saline, which injected through the blood stream or it can be done by surgical implantation in which the stem cells are implanted directly in the pancreas by surgery[14&16].

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COST OF STEM CELL THERAPY

The treatment cost is significantly less of what it cost in western countries. The cost of stem cell therapy for diabetes mellitus in other European countries were approximately in dollars 25000-35000, However in India, it will cost 70-80% less than that. The cost of stem cells therapy depends on various medical factors like type of stem cell therapy and type of cells, number of stem cells required in procedure. Stem cell therapy success rate in India for diabetes mellitus is approximately 70-80% [19].

CONCLUSION

Diabetes is one of the most leading cause of death, there are number of treatment methods are developing in the recent era. Different type of clinical trial are conducted on diabetes patient, in that stem cell therapy is growing process to treat type 2 diabetes. There are numerous potential stem cell therapies are currently used, Mesenchymal stem cells are mostly used to treat type 2 DM. But there is less evidence to prove the effectiveness and safety. There are no proper dosing measures, treatment frequency. For the future, this therapy may help to heal most of the carcinogenic, autoimmune, metabolic diseases with the Mesenchymal stem cells and cord cell. And the treatment is confirmed by the FDA, stem cell must be developed in good manufacturing practice (GMP) conditions. Under GMP measures, a cell line must be made-up so each group of cells is developed in an identical, repeatable, sterile condition. This assurance each cluster of cells has similar properties, and every individual getting an undifferentiated cell treatment gets a related treatment.

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