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RESEARCH ARTICLE

STEM CELL & THEIR ROLE IN DIABETES

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ABSTRACT

Stem cell therapy is miraculous research in the field of medical sciences. It is very useful in future for the treatment of various diseases. According to recent stem cell studies, stem cell can cure many life threatening diseases (such as diabetes, cancer, brain diseases, HIV etc.).[1,2]Stem cell have two specific property one is differentiated into different body cells and another is regenerate the damaged tissue or organ. These properties of stem cell are basically used in the therapy of various diseases, also in treatment of diabetes. Stem cells are obtained from different sources (bone marrow, embryo, skin stem cells etc.). In diabetes stem cell regenerate the damaged Beta cells present in islets of langerhans of pancreas and helps in to cure diabetes. In present time stem cell therapy decreases the uses of anti-diabetic drugs in many patients. In future this therapy will widely use for treatment of various diseases including diabetes.

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INTRODUCTION

STEM CELL

Stem cells are the 'basic cells' of multicellular organism, they are the foundation cells for every organ, tissue and cell of the body which can divide (through mitosis) and differentiate in any type of cell.[1,2] They act as reserve cell with the capacity to grow and multiply to replace dead or damaged adult cells. These cells migrate to injured areas within the body and get transplanted and transform themselves into new tissue cells that replace the damaged ones.[2] Stem cells have the capacity to multiply and renew themselves . Stem cell can form nerve cells, muscle cells and blood cells which cannot multiply themselves and have limited life spans. [1,2,3] Stem cells circulate and function to replace dysfunctional cells, naturally maintaining optimal health. Current medical research is focused on two particular types of stem cells - adult and embryonic. Out of the three types of stem cells, two are able to develop into any type of cell within the human body. These two are called totipotent and pluripotent respectively. Stem cells that are pluripotent have the capability of forming virtually all the possible tissue types found in human beings. These stem cells can only be found in a particular stage (a blastocyst) in human embryos. Multipotent stem cells are partially differentiated, so that they can form a restricted number of tissue types. Multipotent stem cells can be found in the fetus, in numerous adult tissues and umbilical cord blood. The third type of stem cells have less regeneration potential and can only develop into a limited number of other types of cells.

STEM CELL DIFFERENTIATION

First stem cells originate within the developing embryo, develops complete human being via a several steps. A different type of stem cells (embryonic, adult etc.) has different differentiating potential. Such as stem cells from the bone marrow can develop into cardiac muscle as well as liver, brain, nerve, fat and skin tissue. These cells are progenitor cells that lead to creation of new cells and are thus called as generative cells. Hematopoietic stem cells are found in the bone marrow and give rise to all the blood cell types.[4]

Differentiation Potential	Number of cell types	Example of stem cell	Cell types resulting from differentiation
Totipotential	All	Zygote (fertilized egg), blastomere	All cell types
Pleuripotential	All except cells of the embryonic membranes	Cultured human ES cells	Cells from all three germ layers
Multipotential	Many	Hematopoietic cells	skeletal muscle, cardiac muscle, liver cells, all blood cells
Oligopotential	Few	Myeloid precursor	5 types of blood cells (Monocytes, macrophages, eosinophils, neutrophils, erythrocytes)
Quadripotential	4	Mesenchymal progenitor cell	Cartilage cells, fat cells, stromal cells, bone-forming cells
Tripotential	3	Glial-restricted precursor	2 types of astrocytes, oligodendrocytes
Bipotential	2	Bipotential precursor from murine fetal liver	B cells, macrophages
Unipotential	1	Mast cell precursor	Mast cells
Nullipotential	None	Terminally differentiated cell e.g. Red blood cell	No cell division

Table 1. Differential potential ranges from totipotent stem cells to nulli potent cells. [3]

TYPES OF STEM CELLS

On the basis of the sources, stem cells are categories into following types:

- **Embryonic stem cells**
- **Fetal stem cells**
- **Umbilical cord stem cells**
- **Adult stem cells, and**
- **Induced stem cells.**

1) EMBRYONIC STEM CELLS

Embryonic stem cells are generally found in blastocyst. A blastocyst is a pre-implantation embryo. It is developed after five days of the fertilization of an egg by a sperm. It contains the essential material for the development of a complete fetus. The blastocyst is a mostly hollow sphere of cells. In its interior is the inner cell mass, which is composed of 30-34 cells that are referred to by scientists as

pluripotent because they can differentiate into all of the cell types of the body.[1,4,5]

In normal development, the blastocyst would implant in the wall of the uterus to become the embryo and continue developing into a mature organism. Its outer cells would begin to form the placenta and the inner cell mass would begin to differentiate into the progressively more specialized cell types of the body.[1,4]

When the blastocyst is used for stem cell research, scientists remove the inner cell mass and place these cells in a culture dish with a nutrient-rich liquid where they give rise to embryonic stem cells. Embryonic stem cells seem to be more flexible than stem cells found in adults, because they have the potential to produce every cell type in the human body. They are also generally easier to collect, purify and maintain in the laboratory than adult stem cells.

- Sources

In Vitro Fertilization: The source of blastocysts for stem cell research is from in vitro fertilization (IVF) clinics. The process of IVF requires the retrieval of a woman's eggs via a surgical procedure after undergoing an intensive regimen of "fertility drugs", which stimulate her ovaries to produce multiple mature eggs.

When IVF is used for reproductive purposes, doctors typically fertilize all of the donated eggs in order to maximize their chance of producing a viable blastocyst that can be implanted in the womb. Because not all the fertilized eggs are implanted, this has resulted in a large bank of "excess" blastocysts that are currently stored in freezers around the country. The blastocysts stored in IVF clinics could prove to be a major source of embryonic stem cells for use in medical research. However, because most of these blastocysts were created before the advent of stem cell research, most donors were not asked for their permission to use these left-over blastocysts for research. The IVF technique could potentially also be used to produce blastocysts specifically for research purposes.

Nuclear Transfer: It is another technique to produce embryonic stem cells. In this technique nucleus (genetic material) of one cell is transfer by the nucleus of an already differentiated adult cell-for example, a skin cell-into a donated egg that has had its nucleus removed. This egg, which now contains the genetic material of the skin cell, is then stimulated to form a blastocyst from which embryonic stem cells can be derived. The stem cells that are created in this way are therefore copies or "clones" of the original adult cell because their nuclear DNA matches that of the adult cell. According to recent studies nuclear transfer process is not successful in human being, but progress in

animal research suggests that scientists may be able to use this technique to develop human stem cells in the future.

Scientists believe that if they are able to use nuclear transfer to derive human stem cells, it could allow them to study the development and progression of specific diseases by creating stem cells containing the genes responsible for certain disorders.

2) FETAL STEM CELLS

The developing organs and tissues in a fetus contain a relatively large supply of stem cells because they are needed for growth and maturation. The difference between embryonic stem cells and fetal stem cells is the fetal stem cells have matured part of the way to mature cells. For example, if it takes 20 maturation steps for an embryonic stem cell to turn into a mature skin cell, fetal skin cells are at step 10; they are not as mature as adult skin stem cells, but they are past the stage of becoming committed to the liver. There are currently several problems with the therapeutic use of fetal stem cells. First, fetal tissue research is highly controversial. There are significant moral and ethical issues with the use of fetal tissues for research purposes. Second, the numbers of stem cells in fetal tissues may not be sufficient for the therapeutic needs of adults. Thus, methods need to be developed to greatly expand the supply of fetal stem cells if they are to be therapeutically useful. Third, tissue rejection problems similar to those encountered in kidney and heart transplants may limit the usefulness of fetal stem cells. [5]

3) UMBILICAL CORD STEM CELLS

Cells in the umbilical cord are "multipotent" and can give rise to all the cells in normal bone marrow. Scientists are working to discover if cord blood stem cells can multiply and become other types of adult stem cells. For this reason many new parents have their new baby's umbilical cord blood cryopreserved for potential future use. [5]

4) ADULT STEM CELLS-

Adult stem cells are produce after differentiation of pluripotent embryonic stem cells. Adult stem cells are unipotent in nature, produce only one type of cells, generate only their own kind. Such as skin wounds are repaired by skin stem cells, similarly, liver damage is repaired by liver stem cells. Adult stem cells are also known as somatic (means "of the body") stem cells and germline (giving rise to gametes) stem cells, they can be found in children, as well as adults. The use of adult stem cells in research and therapy is not as controversial as the use of embryonic stem cells, because the production of adult stem cells does not require the destruction of an embryo. Additionally, in instances where adult stem cells are obtained from the intended recipient (an

autograft), the risk of rejection is essentially non-existent. Recent studies show that some adult stem cells show pluripotent properties. For example, some experiments have suggested that blood stem cells isolated from adult mice may also be able to produce liver, muscle and skin cells, but these results are not yet proven and have not been demonstrated with human cells. Adult stem cells are found very deep within organs; they are covered by many ordinary cells and may help replenish some of the body's cells when needed. In fact, some adult stem cells are currently being used in therapies. Adult stem cells are generally divided according to their origin such as mesenchymal stem cell (adipose-derived stem cell), endothelial stem cell (endothelial-derived stem cell), dental pulp stem cell (dental pulp-derived stem cells), skin stem cell (skin-derived stem cell) etc.[1,5,6,7]

COMPARISON OF THE DIFFERENT SOURCES OF STEM CELLS

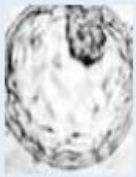
	Embryonic Stem Cells		Adult Stem Cells
			
	In Vitro Fertilization	**Nuclear Transfer**	**Adult Tissues**
Attributes	• can produce all cell types • relatively easy to identify, isolate, maintain, and grow in the laboratory • large source of "excess" blastocysts from IVF clinics	• can produce all cell types • relatively easy to identify, isolate, maintain, and grow in the laboratory • stem cells may be genetically matched to patient	• demonstrated success in some treatments • stem cells may be genetically matched to patient
Limitations	• limited number of cell lines available for federally funded research • risk of creating teratomas (tumors) from implanting undifferentiated stem cells	• not yet achieved with human cells • risk of creating teratomas (tumors) from implanting undifferentiated stem cells	• produce limited number of cell types • not found in all tissues • difficult to identify, isolate, maintain, and grow in the laboratory
Ethical Concerns	• destruction of human blastocysts • donation of blastocysts requires informed consent	• destruction of human blastocysts • donation of eggs requires informed consent • concern about misapplication for reproductive cloning	• no major ethical concerns have been raised

Table 2.Comparison of the different sources of stem cells.[4]

5) INDUCED PLURIPOTENT STEM CELLS

These are not adult stem cells, but rather adult cells (e.g. epithelial cells) reprogrammed to give rise to pluripotent capabilities. Using genetic reprogramming with protein transcription factors, pluripotent stem cells equivalent to embryonic stem cells have been derived from human adult skin tissue**.** [1,8,9,10]

6) MESENCHYMAL STEM CELLS

The reasons behind the inclusion of Mesenchymal stem cells (MSCs) are simply that they are currently the most prolific source of potential therapeutic strategies for human disease and numerous clinical trials are underway using this versatile source of stem cells. MSCs may be isolated from human bone marrow and the first experimental evidence for the existence of a stem cell population in this tissue compartment other than the human stem cells (HSCs) arose in the 1960s.[11]

Developments in stem cell research

YEAR	RESEARCH
1956	First successful bone marrow transplant.
1959	First report of animals (rabbits) produced through IVF into the United States.
1960	Studies on teratocarcinomas in the testes of several strains of mice established that embryonic germ cells are a kind of stem cells.
1968	Edwards and Bavister fertilize the first human egg in vitro.
1970	EC cells injected into mouse blastocysts produce chimeric mice. Cultured stem cell explored as models of embryonic development.
1978	Louise Brown, the first IVF baby, born in England.
1981	Embryonic stem cells are isolated from mouse blastocysts.
1988	Hematopoietic (blood) stem cells from adult mice purified and characterized.
1992	Stem cells are identified in the adult human brain.
1998	The first human embryonic stem cells were isolated.
2002	Pancreatic cells derived from mouse embryonic stem cells cure diabetes in mice.
2004	The type of nerve cell lost in Parkinson's disease is produced from human embryonic stem cells.
2005	Human embryonic stem cells were shown to differentiate into active functioning nerve cells when placed in mouse brains. Scientists also made significant progress in deriving pancreatic cells from adult stem cells.
2006	Derive embryonic stem cells from the morula of a mouse, and embryonic stem cells were first grown without animal products in the culture.
2007	Discovery of induced pluripotent stem cell.
2012	Hair growth in hairless mouse by adult human stem cells.

Table 3. Stem cell research in various years.[4,27]

STEM CELL THERAPY

Stem cell therapy is also called regenerative medicine. According to recent studies stem cells are may be used in various diseases and some diseases are successfully treated by stem cells. Cell-based therapy is an empirical therapy. In this therapy stem cells are induced to differentiate into the specific cell type required to repair the damaged or destroyed cells or tissues. **Treatment can be divided in two types -** Autologous stem cell therapy and Allogenic stem cell therapy [2]

Autologous stem cell therapy

This therapy includes the use of patients own stem cells which are obtained from blood, bone marrow etc.

Allogenic stem cell therapy

In this therapy a person is cured with the help of donated stem cells. However, in number of diseases or disorders, allogenic (foreign) stem cells may be rejected by the body. So far this therapy is not legally accepted in India.[2]

The over view procedure of stem cell therapy in Chaitanya stem center[2]:

- Thorough physical and blood examination will be done by panel of consultants. Patient will be asked to get PET scan and blood investigations to diagnose neurological defect in brain to check eligibility for the therapy.
- Next day stem cell collection will be done. The Chaitanya stem Cell procedure employs autologous adult stem cells and thus these cells are collected from patient own bone marrow. Sample of the same will be send to laboratory where the stem cells will be separated from bone and the quality of the same will be checked.
- First dose of isolated stem cell will be send back to the hospital for intra-thecael / intra-lesional injection. Once the procedure is completed patient will be discharged the next day. However, patients are expected to come for regular follow ups recommended by doctor's.
- Patient will be called for second dose of Stem Cell Injection after 3 month or as per doctor's instructions and if required patient may need to come for a 3rd dose as well. To monitor the progress of stem cell implantation, patient may need to repeat the PET scan.
- The treatment pattern may differ as per patient's status and disease.

Therapy[2]

- Clinical improvements are generally noted for a period of 12-18 months after the start of Stem cell therapy.
- Significant positive change is usually demonstrated on the video after every 12-18 months. Periodically the clinical and psychological evaluation including video recording is also done to note the improvement.
- Parents have seen improvement within four-eight weeks of Stem Cell Therapy. Improved pronunciation, speech and ease of movements, bladder control, reduced irritability, reduced hyperactivity and reduced spasticity are some of the signs of improvement.
- Development in speech, volume and pronunciation in understanding, expression & emotions are other positive signs observed after Stem Cell Therapy.
- Also patients progressively become aware of time as there is development in general sense. Other factors like looks, trunk and control over the neck also significantly improve.

Advantages of Stem Cell Research

- It provides medical benefits in the fields of therapeutic cloning and regenerative medicine.

- It provides great potential for discovering treatments and cures to a plethora of diseases including Parkinson's disease, schizophrenia, Alzheimer's disease, cancer, spinal cord injuries, diabetes and many more.
- Limbs and organs could be grown in a lab from stem cells and then used in transplants or to help treat illnesses.
- It will help scientists to learn about human growth and cell development.
- Scientists and doctors will be able to test millions of potential drugs and medicine, without the use of animals or human testers. This necessitates a process of simulating the effect the drug has on a specific population of cells. This would tell if the drug is useful or has any problems.
- Stem cell research also benefits the study of development stages that cannot be studied directly in a human embryo, which sometimes are linked with major clinical consequences such as birth defects, pregnancy-loss and infertility. A more comprehensive understanding of normal development will ultimately allow the prevention or treatment of abnormal human development.
- Another advantage of stem cell research is that it holds the key to reversing the effects of aging and prolonging our lives. Stem cell research has already found many treatments that help in slowing the aging process, and a bonus of further stem cell research is a possible 'cure' for aging altogether.
- An advantage of the usage of adult stem cells to treat disease is that a patient's own cells could be used to treat a patient. Risks would be quite reduced because patients' anti bodies would not reject their own cells.
- Embryonic stem cells can develop into any cell types of the body, and may then be more versatile than adult stem cells.

ROLE OF STEM CELLS IN DIABETES

Diabetes mellitus (DM) – It is a metabolic disorder characterized by hyperglycemia, glycosuria, hyperlipidemia, negative nitrogen balance and sometimes ketonaemia.

According to WHO, the term diabetes mellitus describes a metabolic disorder of multiple etiology characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both **(WHO, 1999)**. A widespread pathological change is thickening of capillary basement membrane, increase in vessel wall matrix and cellular proliferation resulting in vessel wall matrix and cellular proliferation resulting in vascular complications like lumen narrowing, early atherosclerosis, sclerosis of glomerular capillaries, retinopathy, neuropathy and peripheral vascular insufficiency**.**[14]It is a syndrome of impaired carbohydrate fat and protein, metabolism caused by either lack of insulin secretion or decreased sensitivity of the tissues to insulin.[13]

For decades, diabetes researchers have been searching for ways to replace the insulin-producing cells of the pancreas that are destroyed by a patient's own immune system. Diabetes is the seventh leading cause of death in the United States today, with nearly 200,000 deaths reported each year. The American Diabetes Association estimates that nearly 16 million people, or 5.9 percent of the United States population, currently have diabetes. [14]

Specifically, there are three types of diabetes [12,27]:

The etiological types designate defects, disorders or processes which often result in diabetes mellitus.

Type 1 (IDDM, beta–cell destruction, usually leading to absolute insulin deficiency)

Type 1 indicates the processes of beta–cell destruction that may ultimately lead to diabetes mellitus in which “insulin is required for

survival" to prevent the development of ketoacidosis, coma and death. An individual with a Type 1 process may be metabolically normal before the disease is clinically manifest, but the process of beta–cell destruction can be detected. Many patients are diagnosed when they are older than 20 years of age. In this disease, the body makes little or no insulin. For treating diabetes of this kind, daily injections of insulin are required. The exact cause however is unknown. Genetics, viruses and autoimmune problems may play a role.

Type 2 (NIDDM, predominantly insulin resistance with relative insulin deficiency or predominantly an insulin secretory defect with/without insulin resistance)

Two metabolic defects that are characterize type-2 diabetes mellitus are:

1. A derangement in β-cell secretion of insulin
2. A decrease response of peripheral tissue to respond to insulin (Insulin resistance).

NIDDM more common than type 1 and most diabetics suffer from this type. Usually occurring during adulthood, there are young people in India today that are increasingly being diagnosed with this disease. Many people with type 2 diabetes don't even know they are suffering from it. Though this is a serious condition, Type 2 diabetes has become far more common due to increasing obesity and failure to exercise. Treating such a condition thus becomes necessary.

Gestational Diabetes Mellitus- Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance with onset or first diagnosis during pregnancy and diagnosed in the second and third trimester. Glucose tolerance return to normal within 6 weeks after ends. Gestational diabetes mellitus occurs in approximately 2-5% of all pregnancies and is fully treatable but requires careful medical supervision throughout the pregnancy. About 20-25% of affected women develop type-2 diabetes later in life **(American Optometric Association, 2002)**.

There are many risk factors for type 2 diabetes, including:

- Age over 45 years
- A parent, brother or sister with diabetes
- Gestational diabetes or delivering a baby weighing more than 9 pounds
- Heart disease
- High blood cholesterol level
- Obesity
- Not getting enough exercise
- Polycystic ovary disease (in women)
- Previous impaired glucose tolerance
- Some ethnic groups (particularly African Americans, Native Americans, Asians, Pacific Islanders and Hispanic Americans)

Development of the Pancreas

Before discussing cell-based therapies for diabetes, it is important to understand how the pancreas develops. In mammals, the pancreas contains three classes of cell types: the endocrine cells, the acinar cells, and the ductal cells. The endocrine cells produce the hormones glucagon, somatostatin, pancreatic polypeptide (PP) and insulin, which are secreted into the blood stream and help the body regulate sugar metabolism. The acinar cells are part of the exocrine system, which manufactures digestive enzymes, and ductal cells from the pancreatic ducts, which connect the acinar cells to digestive organs. [15]

In humans, the pancreas develops as an outgrowth of the duodenum, a part of the small intestine. The cells of both the exocrine system—the acinar cells—and of the endocrine system—the islet cells—seem to originate from the ductal cells during development. During development these endocrine cells emerge from the pancreatic ducts and form aggregates that eventually form, which is known as Islets of Langerhans. In humans, there are four types of islet cells: the insulin-producing beta cells; the alpha cells which produce glucagon; the delta cells which secrete somatostatin and the PP-

cells which produce pancreatic polypeptide. The hormones released from each type of islet cell have a role in regulating hormones released from other islet cells.

The pancreas is located in the abdomen, adjacent to the duodenum (the first portion of the small intestine). A cross-section of the pancreas shows the islet of Langerhans which is the functional unit of the endocrine pancreas. Encircled is the beta cell that synthesizes and secretes insulin. Beta cells are located adjacent to blood vessels and can easily respond to changes in blood glucose concentration by adjusting insulin production. Insulin facilitates uptake of glucose, the main fuel source, into cells of tissues such as muscle. During fetal development, new endocrine cells appear to arise from progenitor cells in the pancreatic ducts. Many researchers maintain that some sort of islet stem cell can be found intermingled with ductal cells during fetal development and that these stem cells give rise to new endocrine cells as the fetus develops. Ductal cells can be distinguished from endocrine cells by their structure and by the genes they express. For example, ductal cells typically express a gene known as *cytokeratin-9 (CK-9)*, which encodes a structural protein. Beta islet cells, on the other hand, express a gene called PDX-1 which encodes a protein that initiates transcription from the insulin gene. These genes, called cell markers, are useful in identifying particular cell types. [13,14]

Following birth and into adulthood, the source of new islet cells is not clear, and some controversy exists over whether adult stem cells exist in the pancreas. Some researchers believe that islet stem cell-like cells can be found in the pancreatic ducts and even in the islets themselves. Others maintain that the ductal cells can differentiate into islet precursor cells, while others hold that new islet cells arise from stem cells in the blood. Researchers are using several approaches for isolating and cultivating stem cells or islet precursor cells from fetal and adult pancreatic tissue. In addition, several new promising studies indicate that insulin-producing cells can be cultivated from embryonic stem cell lines. [13,14]

Development of Cell-Based Therapies for Diabetes

In developing a potential therapy for patients with diabetes, researchers hope to develop a system that meets several criteria. Ideally, stem cells should be able to multiply in culture and reproduce themselves exactly. That is, the cells should be self-renewing. Stem cell should also be able to differentiate to produce the desired kind of cell. For diabetes therapy, it is not clear whether it will be desirable to produce only beta cells—the islet cells that manufacture insulin—or whether other types of pancreatic islet cells are also necessary. Studies by BernatSoria and colleagues indicate that isolated beta cells—those cultured in the absence of the other types of islet cells—are less responsive to changes in glucose concentration than intact islet clusters made up of all islet cell types[20]. Islet cell clusters typically respond to higher-than-normal concentrations of glucose by releasing insulin in two phases: a quick release of high concentrations of insulin and a slower release of lower concentrations of insulin. In this manner the beta cells can fine-tune their response to glucose. Extremely high concentrations of glucose may require that more insulin be released quickly, while intermediate concentrations of glucose can be handled by a balance of quickly and slowly released insulin.

Isolated beta cells, as well as islet clusters with lower-than-normal amounts of non-beta cells, do not release insulin in this biphasic manner. Instead insulin is released in an all-or-nothing manner, with no fine-tuning for intermediate concentrations of glucose in the blood. Therefore, many researchers believe that it will be preferable to develop a system in which stem or precursor cell types can be cultured to produce all the cells of the islet cluster in order to generate a population of cells that will be able to coordinate the release of the appropriate amount of insulin to the physiologically relevant concentrations of glucose in the blood.[15,16]

Fetal Tissue as Source for Islet Cells

Several groups of researchers are investigating the use of fetal tissue as a potential source of islet progenitor cells. For example, using mice, researchers have compared the insulin content of implants from several sources of stem cells—fresh human fetal pancreatic tissue, purified human islets, and cultured islet tissue. They found that insulin content was initially higher in the fresh tissue and purified islets. However, with time, insulin concentration decreased in the whole tissue grafts, while it remained the same in the purified islet grafts. When cultured islets were implanted, however, their insulin content increased over the course of three months. The researchers concluded that precursor cells within the cultured islets were able to proliferate (continue to replicate) and differentiate (specialize) into functioning islet tissue, but that the purified islet cells (already differentiated) could not further proliferate when grafted. Importantly, the researchers found, however, that it was also difficult to expand cultures of fetal islet progenitor cells in culture. [17,18]

Adult Tissue as Source for Islet Cells

Many researchers have focused on culturing islet cells from human adult cadavers for use in developing transplantable material. Although differentiated beta cells are difficult to proliferate and culture, some researchers have had success in engineering such cells to do this. For example, Fred Levine and his colleagues at the University of California, San Diego, have engineered islet cells isolated from human cadavers by adding to the cells' DNA special genes that stimulate cell proliferation. However, because once such cell lines that can proliferate in culture are established, they no longer produce insulin. The cell lines are further engineered to express the beta islet cell gene, PDX-1, which stimulates the expression of the insulin gene. Such cell lines have been shown to propagate in culture and can be induced to differentiate to cells, which produce insulin. When transplanted into immune-deficient mice, the cells secrete insulin in response to glucose. The researchers are currently investigating whether these cells will reverse diabetes in an experimental diabetes model in mice.[19,20]

These investigators report that these cells do not produce as much insulin as normal islets, but it is within an order of magnitude. The major problem in dealing with these cells is maintaining the delicate balance between growth and differentiation. Cells that proliferate well do not produce insulin efficiently, and those that do produce insulin do not proliferate well. According to the researchers, the major issue is developing the technology to be able to grow large numbers of these cells that will reproducibly produce normal amounts of insulin.[21]

Another promising source of islet progenitor cells lies in the cells that line the pancreatic ducts. Some researchers believe that multipotent (capable of forming cells from more than one germ layer) stem cells are intermingled with mature, differentiated duct cells, while others believe that the duct cells themselves can undergo a differentiation, or a reversal to a less mature type of cell, which can then differentiate into an insulin-producing islet cell.

Bonner-Weir and her colleagues are working with primary cell cultures from duct cells and have not established cells lines that can grow indefinitely.[28] However the cells can be expanded. According to the researchers, it might be possible in principle to do a biopsy and remove duct cells from a patient and then proliferate the cells in culture and give the patient back his or her own islets. This would work with patients who have type-1diabetes and who lack functioning beta cells, but their duct cells remain intact. However, the autoimmune destruction would still be a problem and potentially lead to destruction of these transplanted cells. Type 2 diabetes patients might benefit from the transplantation of cells expanded from their own duct cells since they would not need any immunosuppression. However, many researchers believe that if there is a genetic component to the death of beta cells, then beta cells derived from ductal cells of the

same individual would also be susceptible to autoimmune attack.[22]

Joel Habener has also looked for islet-like stem cells from adult pancreatic tissue. He and his colleagues have discovered a population of stem-like cells within both the adult pancreas islets and pancreatic ducts. These cells do not express the marker typical of ductal cells, so they are unlikely to be ductal cells, according to Habener. Instead, they express a marker called nestin, which is typically found in developing neural cells. The nestin-positive cells do not express markers typically found in mature islet cells. However, depending upon the growth factors added, the cells can differentiate into different types of cells, including liver, neural, exocrine pancreas, and endocrine pancreas, judged by the markers they express, and can be maintained in culture for up to eight months. [23]

Source	Type of stem cells
Adult stem cells	Hematopoietic stem cells , Mesenchymal stem cells
Umbilical cord stem cells	Cord blood or cord wall mesenchymal stem cells, Embryonic-like stem cells
Embryonic stem cells	Blastocyst- derived embryonic stem cells
Pancreatic cells	Pancreatic stem cells, Reprogrammed adult pancreatic exocrine cell

Table 4. Types of stem cells with potential to treat type 1 diabetes mellitus. [24]

Mechanism of stem cells in diabetes

From the clinical research, Mesenchymal stem cells (MSCs) transplantation in patients with diagnosed diabetes mellitus (DM) resulted in the majority of patients becoming insulin producing and better control of blood sugar levels.

1. Stem cell can repair the injured islet β cells.
2. Part of the stem cells differentiate into vascular endothelial cells and then improve the blood supply of pancreas and recover the function of islet β cells.
3. Stem cells migrate to the injured part of the pancreas and differentiate into islet β cells;
4. Stem cells have immune-regulation function.

Autologous (originating from your own body) stem cell therapy for diabetes II does just that - drug free. It fights diabetes at its roots, reducing hyperglycemia and its associated complications. Cord mesenchymal cell transplantation also, have much better regeneration potentials. Stem cells transplanted by IV injection (intravenous injection) and interventional therapy to inject stem cells into the pancreas directly.

Diabetes patients are usually treated by injecting the stem cells into the pancreatic artery via catheter. Patients, who cannot safely undergo the catheterization procedure such as those with kidney problems, are offered an only intravenous stem cell implantation. Its observed that secondary complications (like Neuropathy, Kidney effect, Vascular changes leading to gangrene, Retinopathy, etc.) shows early recovery, even before change in insulin requirement.

Achieved results are seen as follows:

According to studies of Stem Cell Department was co-founded in 2003 by Beijing Tiantan Hospital, Beijing Neurological Institute and the Wujing General Hospital of Chinese People's Armed Police Forces under the leadership of Dr. Wang Zhongcheng, who served as the Chairman of the Committee of Neurosurgeons of the Chinese Academy of Medical Sciences.Achieved results in the study are as follows:

- 62.9% of patients could decrease their insulin injections & hypoglycemic medications by more than 50%
- 3.7% of Type 1 and 11.1% of Type 2 patients could completely stop insulin injections
- improved pancreatic islet function
- stable blood glucose level throughout the day

- improved symptoms of diabetes associated complications such as diabetic retinopathy, diabetic nephropathy, diabetic macro vascular pathological changes, diabetic peripheral neuropathy and diabetic autonomic neuropathy. [25]

Other uses of stem cells

Like in diabetes stem cell used in many diseases. According to recent studies its regeneration ability is used in the treatment of various diseases. Animal studies show that stem cell can regenerate or repair the many organ/tissue of body. So at present time this study is continued in humans for treatment of various diseases. Diseases cured by the stem cells:

- Spinal cord injury
- Heart disease
- **Lung diseases**
- **Arthritis**
- **Sickle cell anemia**
- **Renal diseases**
- Parkinson's
- Infertility
- Brain Damage
- Diabetes
- Cancer
- Hematopoiesis (blood cell formation)
- Baldness
- Deafness
- Vision Defects

CONCLUSION

Till date, the recent advancements and researches have demonstrated that stem cell therapy helps in regeneration of beta cell, present in islet of langerhans of pancreas, and improves blood supply of damaged pancreas. Hence in future, stem cell therapy can cure diabetes with minimal or no adverse effect. Stem cell research focuses on stem cells, which have a capacity to regenerate. Stem cells circulate and function to replace dysfunctional cells, naturally maintaining optimal health. Current medical research is focused on two particular types of stem cells - adult and embryonic. Totipotent and pluripotent stem cells are able to develop into any type of cell within the human body.

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