ISSN: 2320 - 4230

Journal of Drug Discovery and Therapeutics 1 (4) 2013, 28-33

REVIEW ARTICLE

TREATMENT AND MANAGEMENT OF DIABETES WITH STEM CELL THERAPY: A NEWER SCIENTIFIC APPRAOCH

Prof. Satyanand Tyagi*[1], Patel Chirag J[2], Dr. Ruchika Nandha[3], Dr. Kavita Sekhri[3], Dr. Suruchi Aditya[3], Dr. Ravpreet Singh[4], Anil Kumar Gupta[5], Dr. Shweta Tyagi[6]

*[1]President & Founder, Tyagi Pharmacy Association & Scientific Writer (Pharmacy), Chattarpur, New Delhi, India-110074.
[2]Editor-in-Chief, Tyagi Pharmacy Association (TPA) & Scientific Writer (Pharmacy), Chattarpur, New Delhi, India-110074.
[3]Department of Pharmacology, Dr. Harvansh Singh Judge Institute of Dental Sciences, Chandigarh, Punjab, India-160014.
[4]P.G. Research Scholar, Department of Homoeopathy, Sri Sai Nath Post Graduate Insti. of Homoeopathy, Allahabad, Uttar Pradesh, India-211002.
[5]Research Scholar, Bhagwant University, Institute of Pharmacy & Research Center, Ajmer, Rajasthan, India-305004
[6]Sri Sri College of Ayurvedic Science and Research Hospital, Kanakapura Road, Udayapura, Bangalore, Karnataka, India-560082.

ABSTRACT

Diabetes is usually a lifelong (chronic) disease in which there are high levels of sugar in the blood. Diabetes, often referred to by doctors as diabetes mellitus, describes a group of metabolic diseases in which the person has high blood glucose (blood sugar), either because insulin production is inadequate, or because the body's cells do not respond properly to insulin, or both. Patients with high blood sugar will typically experience polyuria (frequent urination); they will become increasingly thirsty (polydipsia) and hungry (polyphagia). Insulin, a hormone produced by the pancreas helps in the control of blood sugar. While Diabetes can be caused by too little insulin, resistance to insulin or both, its treatment becomes mandatory for patients as a large part of the Indian population is gradually being detected with high blood sugar. Stem cells are mother cells that have the potential to become any type of cell in the body. One of the main characteristics of stem cells is their ability to self-renew or multiply while maintaining the potential to develop into other types of cells. Stem cells can become cells of the blood, heart, bones, skin, muscles, brain etc. Within recent years, stem cell research has become a very important part of the scientific understanding of type 1 diabetes. Research has demonstrated that stem cells can be grown in the lab. In 2004, the University of Pittsburgh grew insulin producing beta cells by introducing two genes 'cdk' and 'cyclin d' via a virus. The researchers were able to deactivate the virus and also prevent stem cells from growing further. The research could lead to a better availability of beta cells for future research purposes. Type 1 and type 2 diabetes results when beta cells in the pancreas fail to produce enough insulin, the hormone that regulates blood sugar. One approach to treating diabetes is to stimulate regeneration of new beta cells. The current short communication elucidate about probable treatment of diabetes with the help of stem cell therapy.

KEY-WORDS: Diabetes, Stem cells, Beta cells, Insulin.

INTRODUCTION:

Diabetes, often referred to by doctors as diabetes mellitus, describes a group of metabolic diseases in which the person has high blood glucose (blood sugar), either because insulin production is inadequate, or because the body's cells do not respond properly to insulin, or both. Patients with high blood sugar will typically experience polyuria (frequent urination), they will become increasingly thirsty (polydipsia) and hungry (polyphagia).

There are three types of diabetes[1]:

1. Type 1 Diabetes:

In this condition, the body does not produce insulin. Some people may refer to this type as insulin-dependent diabetes, juvenile diabetes, or early-onset diabetes.

People usually develop type 1 diabetes before their 40th year, often in early adulthood or teenage years. Type 1 diabetes is nowhere near as common as type 2 diabetes. Approximately 10% of all diabetes cases are type 1. Patients with type 1 diabetes will need to take insulin injections for the rest of their life. They must also ensure proper blood-glucose levels by carrying out regular blood tests and following a special diet. Between 2001 and 2009, the prevalence of type 1 diabetes among the under 20s in the USA rose 23%, according to SEARCH for Diabetes in Youth data issued by the CDC (Centers for Disease Control and Prevention)[2].

2. Type 2 Diabetes:

In this condition, the body does not produce enough insulin for proper function, or the cells in the body do not react to insulin (insulin resistance). Approximately 90% of all cases of diabetes worldwide are of this type. Some people may be able to control their type 2 diabetes symptoms by losing weight, following a healthy diet, doing plenty of exercise, and monitoring their blood glucose levels. However, type 2 diabetes is typically a progressive

*Corresponding author: Prof. Satyanand Tyagi

disease - it gradually gets worse - and the patient will probably end up have to take insulin, usually in tablet form. Overweight and obese people have a much higher risk of developing type 2 diabetes compared to those with a healthy body weight. People with a lot of visceral fat, also known as central obesity, belly fat, or abdominal obesity, are especially at risk. Being overweight/obese causes the body to release chemicals that can destabilize the body's cardiovascular and metabolic systems.

3. Gestational Diabetes

This type affects females during pregnancy. Some women have very high levels of glucose in their blood, and their bodies are unable to produce enough insulin to transport all of the glucose into their cells, resulting in progressively rising levels of glucose. Diagnosis of gestational diabetes is made during pregnancy. The majority of gestational diabetes patients can control their diabetes with exercise and diet. Between 10% to 20% of them will need to take some kind of blood-glucose-controlling medications. Undiagnosed or uncontrolled gestational diabetes can raise the risk of complications during childbirth. The baby may be bigger than he/she should be. Scientists from the National Institutes of Health and Harvard University found that women whose diets before becoming pregnant were high in animal fat and cholesterol had a higher risk for gestational diabetes, compared to their counterparts whose diets were low in cholesterol and animal fats[3].

DIABETES COMPLICATIONS:[4]

Two types of diabetes complications (**Figure 1**) were observed:

1. Macrovascular complication
2. Microvascular complication

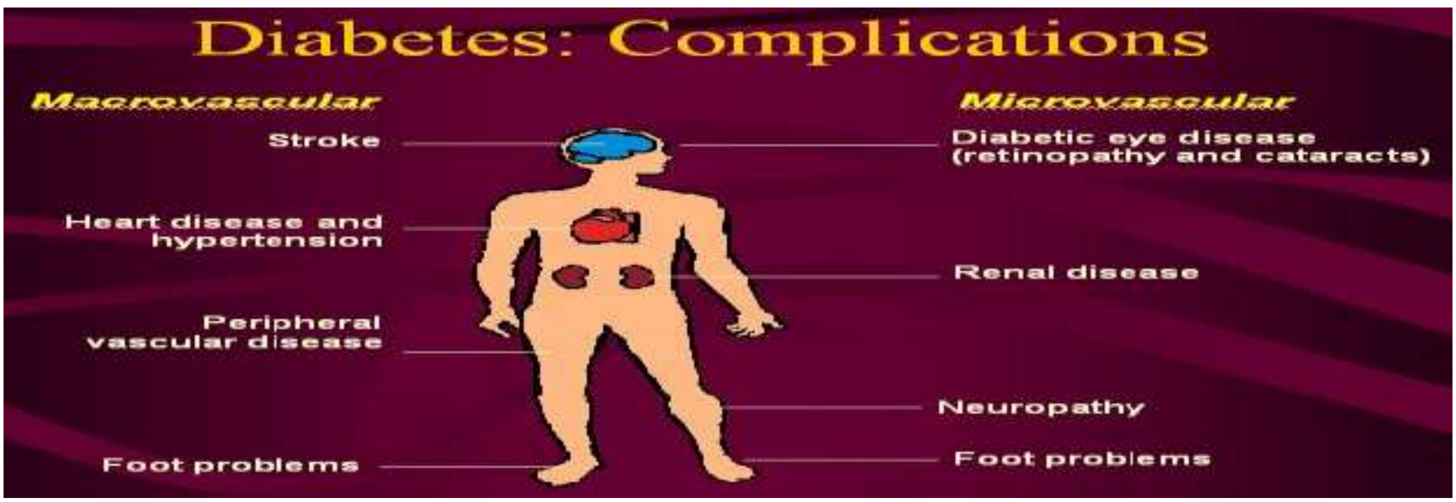

Figure 1: Diabetes Complications[4]

STEM CELLS:

Stem cells are biological cells found in all multicellular organisms, that can divide (through mitosis) and differentiate into diverse specialized cell types and can self-renew to produce more stem cells. In mammals, there are two broad types of stem cells (Figure 2): embryonic, which are isolated from the inner cell mass of blastocysts, and adult stem cells, which are found in various tissues. In adult organisms, stem cells and progenitor cells act as a repair system for the body, replenishing adult tissues. In a developing embryo, stem cells can differentiate into all the specialized cells (these are called pluripotent cells), but also maintain the normal turnover of regenerative organs, such as blood, skin, or intestinal tissues.

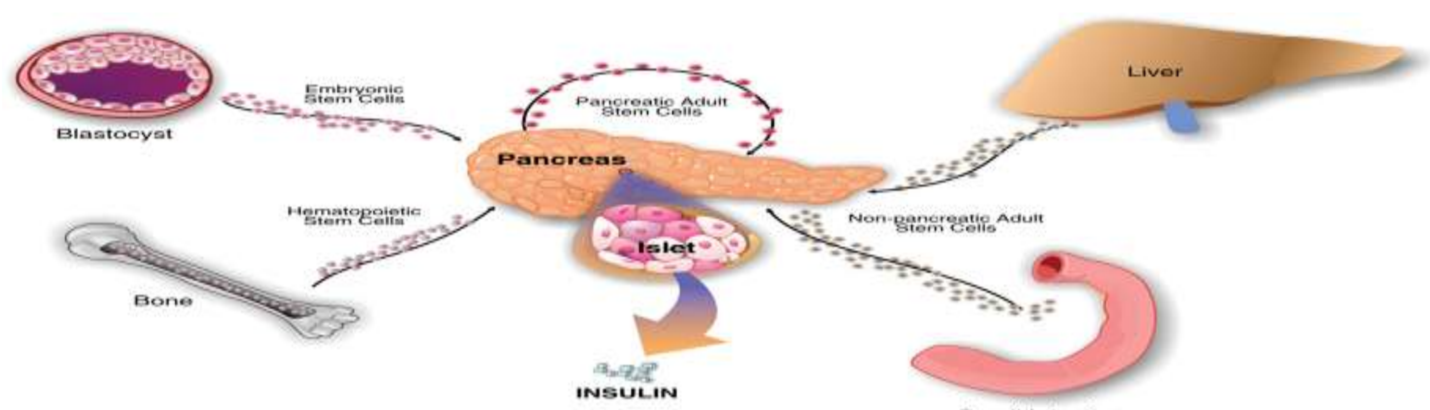

Figure 2: Multiple sources of stem cells that have been developed to produce insulin[5]

There are three accessible sources of autologous adult stem cells in humans:

1. Bone marrow, which requires extraction by harvesting, that is, drilling into bone (typically the femur or iliac crest),
2. Adipose tissue (lipid cells), which requires extraction by liposuction, and
3. Blood, which requires extraction through pheresis, wherein blood is drawn from the donor (similar to a blood donation), passed through a machine that extracts the stem cells and returns other portions of the blood to the donor.

Stem cells can also be taken from umbilical cord blood just after birth. Of all stem cell types, autologous harvesting involves the least risk. By definition, autologous cells are obtained from one's own body, just as one may bank his or her own blood for elective surgical procedures. Highly plastic adult stem cells are routinely used in medical therapies, for example in bone marrow transplantation. Stem cells can now be artificially grown and transformed (differentiated) into specialized cell types with characteristics consistent with cells of various tissues such as muscles or nerves through cell culture. Embryonic cell lines and autologous embryonic stem cells generated through therapeutic cloning have also been proposed as promising candidates for future therapies[6].

Research into stem cells grew out of findings by Ernest A. McCulloch and James E. Till at the University of Toronto in the 1960s[7, 8].

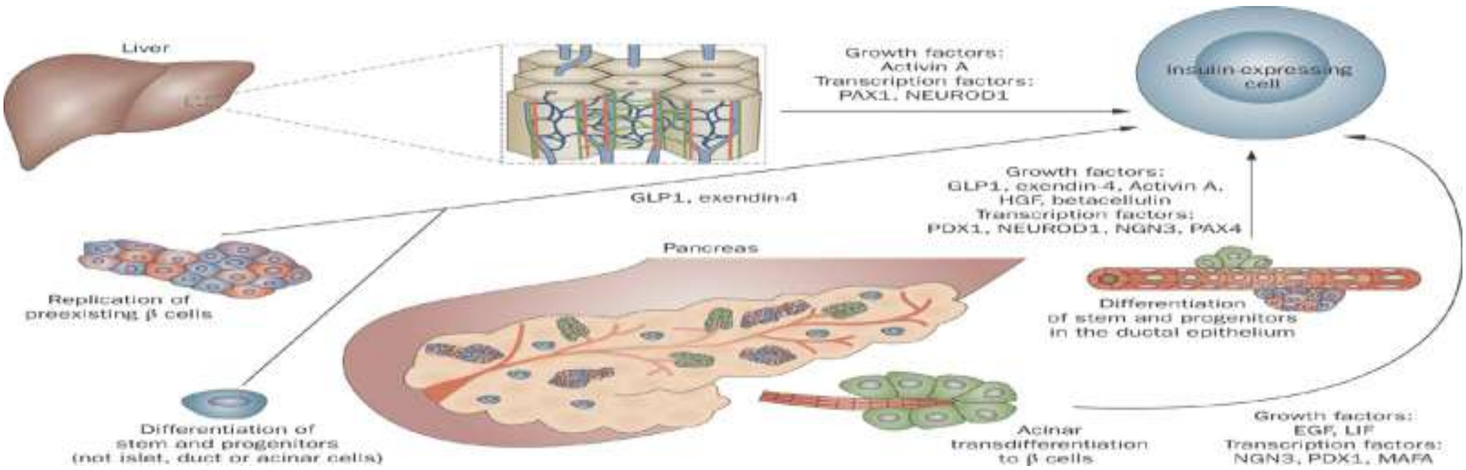

Figure 3: Strategies to obtain β cells from organ-specific stem or progenitor cells[9]

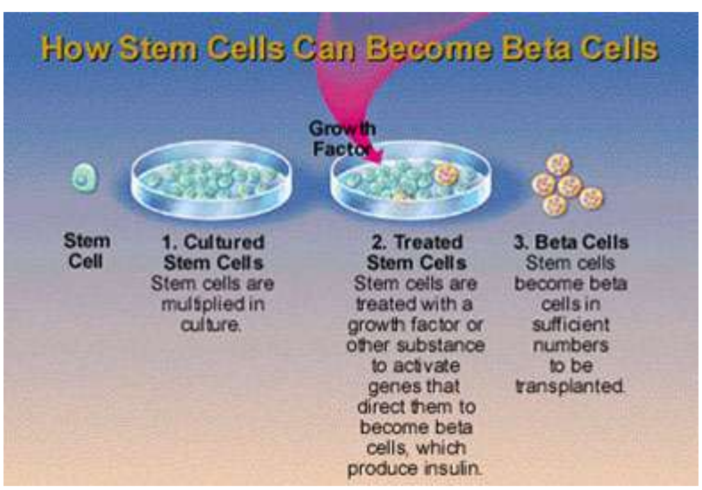

Figure 4: Process of stem cell to become beta cell[10]

CLINICAL APPLICATIONS OF STEM CELLS

Medical researchers anticipate that adult and embryonic stem cells will soon be able to treat cancer, Type 1 diabetes mellitus, Parkinson's disease, Huntington's disease, Celiac Disease, cardiac failure, muscle damage and neurological disorders, and many others (Figure 5). Nevertheless, before stem cell therapeutics can be applied in the clinical setting, more research is necessary to understand stem cell behavior upon transplantation as well as the mechanisms of stem cell interaction with the diseased/injured microenvironment[11]. Medical researchers believe that stem cell therapy (Figure 6) has the potential to dramatically change the treatment of human disease. A number of adult stem cell therapies already exist, particularly bone marrow transplants that are used to treat leukaemia[12].

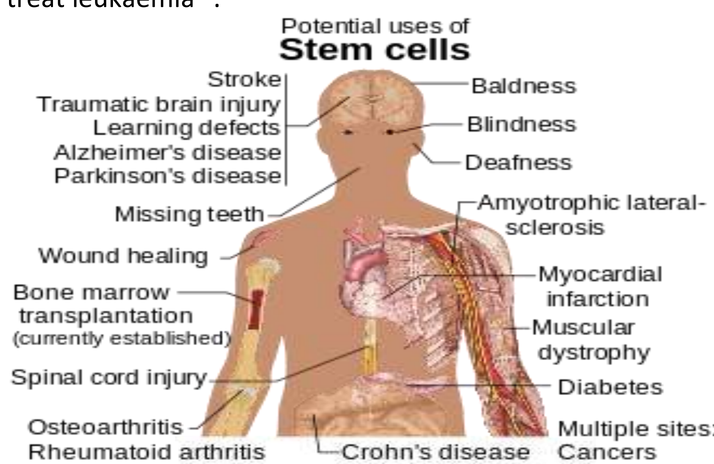

Figure 5: Diseases and conditions where stem cell treatment is promising or emerging[13].

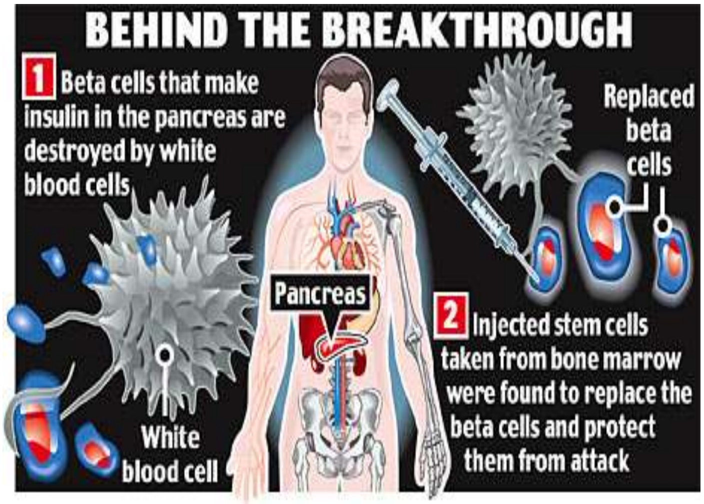

Figure 6: Stem cell therapy[14]

DIABETES AND STEM CELLS:

Patients with type 1 diabetes take insulin shots a few times a day after checking their blood sugar. But a normal pancreas tests the blood sugar every second of the day and adjusts the precise amount of insulin needed. So the problem is that most of the day, the diabetes patient's blood sugar is out of control[15].

Although researchers have made enormous strides toward using stem cells as a potential treatment for type 1 diabetes, there are a number of issues that need to be addressed. These include concerns of both a scientific and societal nature.

Issues related to the use of stem cells in the treatment of type 1 diabetes

1. Potential risks, including teratomas.
2. Challenges related to the transplantation of isolated cells lacking vascular and neural support.
3. Need for immunosuppression.
4. Ethical acceptance.
5. Engraftment of a non-marginal mass of insulin-producing cells for human use (exceeding 15 000 IE/kg of body weight).

First, before any new treatment is used in the human population, it of course needs to undergo rigorous testing and screening for potential side effects. This concern for safety is probably even more heightened when it comes to stem cells. One complication that has already arisen in the mouse models is the formation of teratomas with the potential for malignancy.

This is especially a concern with ESCs (Embryonic Stem Cell), where groups have already observed teratoma formation when grafts were histologically assessed. These tumors form due to the implantation of undifferentiated cell populations into an immunodeficient host; such as would be the case if these cells were introduced into a patient on necessary immunosuppressives. It would be difficult to treat patients with a cell-replacement product for diabetes if it could not be demonstrated to be safe with respect to teratoma formation. Future protocols will therefore need some form of purification or screening step in order to eliminate and screen for the presence of unsafe cells respectively. Of course, if the replacement therapy could be administered without immunosuppressive drugs, the possibility of teratoma formation would no doubt be lessened. The pancreas is a very complex organ with many functions both endocrine and exocrine in nature. Endogenous β-cells develop through a regulated pathway to eventually become the insulin-producing cells which regulate euglycaemia. The mature cells are part of an integrated milieu of cells and cellular signals together with their cellular products. Even the islets transplanted in current clinical islet-transplant programmes contain β-cells along with α- and δ-cells. In addition, endogenous islets are situated in a complex array of vascular and neural supports. How will stem-cell-derived products behave once transplanted? Depending on the transplant site, will they be able to develop these same vascular and neural connections? Even though some groups have shown the production of glucagon and somatostatin in their cell populations, how will these cells interact once transplanted into an unfamiliar environment? Will it be necessary to have a complete islet structure with the appropriate endocrine hormone composition or will it be sufficient to have appropriate numbers of β-cells?

Recent studies have demonstrated that purified β-cell preparations are sufficient to treat the diabetic condition in rodents. In addition, it is likely that β-cells are able to adapt to changes in their glucose environment and adapt to insulin resistance through both neogenesis and cell replication. Will stem-cell-derived β-cells have these abilities or, even worse, will increased insulin resistance cause these β-cells to expand uncontrollably? Further studies will no doubt need to address these issues. Although a cellular-based replacement therapy for diabetes would overcome one of the major limitations of our current islet transplantation protocol, it is still likely to be subject to the other major limitation.

Unless a protocol is developed where stem cells are derived from a patient's own cellular population (and even here the issue of the autoimmune insult which caused the disease needs to be addressed), some form of immunosuppression or an immuno-isolation delivery strategy will be required. Clearly our knowledge of the immune system and therapies targeted at diminishing its effects has made great strides, but patients are faced with unpleasant and, at times, unbearable side effects from immunosuppressive agents. Thus, although stem cells could conceivably circumvent the need to rely on organ donation for a source of insulin-producing tissue, they may do nothing to relieve the toxicity associated with the post-implantation drug therapy, unless additional immunomodulatory regulatory stem cells are co-transplanted or specific tolerization strategies are developed. Any future stem-cell-related therapies will no doubt be facilitated by improvements in the tolerance of our current anti-immune therapies. Underlying this point is the need to continue with the current research into islet transplantation, as any further advances made there will no doubt have a positive impact upon the development of any cellular-based diabetes therapy. When considering current clinical islet transplantation programmes another interesting issue arises.

Current guidelines employ a minimal islet implant mass of 10000 IE (islet equivalent)/kg of body weight, usually obtained by harvesting two pancreases. Even with this amount of islets, most patients need to return to a small amount of insulin at the 2–3-year mark. It still remains to be seen how stem cells can compare, in terms of insulin production and potency, to this amount of islets. Although Kroon et al. have stated that their stem-cell-derived products are achieving a production rate of C-peptide equivalent to 3000–5000 human islets in their mouse model; this is far short of the levels needed to support an adult human. The scale-up potential of stem cells will, therefore, need to be studied further to provide an excess of transplanted cellular reserve. The last issue, and certainly by no means the least important, is the intense ethical debate that forms from any discussion of stem cells. Beginning with the cloning of Dolly the sheep in 1997, cultural fires have ignited with any mention of cloning or genetic engineering. These fires have now spread to the field of stem cell research. Here, it appears the issues revolve mainly around ESCs and their derivation. In short, ESCs are usually derived from unused embryos at in vitro fertilization clinics.

Full informed consent needs to be given by the donor before these cells can be used. Unfortunately, the embryo, in most cases, needs to be destroyed to harvest the cells it contains. It appears that the majority of the controversy develops from this derivation process and the question of when life actually begins. On the one hand are those that believe that stem cell research violates the sanctity of life. They are of the mind that life is inviolable and begins when a sperm fertilizes an egg.

They are in direct contrast with those that take a more utilitarian view on the issue where the potential benefits, in terms of cellular therapies for medical conditions, outweigh the potential costs. Although this debate continues, the full extent of its impact on research using stem cells remains to be seen. Even though adult stem cells will probably avoid much of the negative publicity generated by their embryonic cousins, any potential clinical uses involving stem cells will need to be accompanied by a thorough explanation of their derivation. Although unlikely to end the debate, it will hopefully ease some of the tension that has built up around this topic. A longer-term solution to the human ESC ethical dilemma will probably be the induced pluripotent stem cell approach. In this case, adult cells are reprogrammed to the pluripotent state to be subsequently differentiated to functional β-cells. The further safety concerns associated with ex vivo gene therapy with oncogenes which, together with a better understanding of the genetic and epigenetic stability, adds a further safety burden probably to be solved in the future[5].

STEM CELLS USE IN ISLET CELL TRANSPLANTS[16, 17]

To cure type 1 diabetes, stem cell replacement needs to be more than simply a case of swapping insulin-producing cells from a healthy pancreas with those destroyed by diabetes in a diabetic patient. Numerous complications preclude this as a simple treatment. Islet cell transplants are one form of procedure that has proven effective. In type 1 diabetes, the body's immune system becomes programmed to attack the beta cells, so the patient must take immuno-suppressant drugs to prevent this happening. In the future, it may be possible to grow islet cells from patient's existing islet cells, however, a patient with type 1 diabetes would still need immune suppressants to prevent the cells being destroyed.

Curative therapy for diabetes mellitus mainly implies replacement of functional insulin-producing pancreatic β cells, with pancreas or islet-cell transplants. However, shortage of donor organs spurs research into alternative means of generating β cells from islet expansion, encapsulated islet xenografts, human islet cell-lines, and stem cells. Stem cell therapy here implies the replacement of diseased or lost cells from progeny of pluripotent or multipotent cells. Both embryonic stem cells (derived from the inner cell mass of a blastocyst) and adult stem cells (found in the postnatal organism) have been used to generate surrogate β cells or otherwise restore β cell functioning.

CONCLUSION:

Diabetes mellitus (DM) is one of the prevailing hormonal diseases. It is often called a "non-infectious epidemic disease of the 21st century". 200 million people have diabetes worldwide, and their number is increasing.
By 2025, the number of diabetes mellitus sufferers is expected to increase by 50%. Diabetes mellitus is characterized by a high blood sugar (glucose) level resulting from either insufficient insulin production in the body (type

I diabetes) or body cells improper response to the produced insulin (type II diabetes). Stem cell treatment of diabetes leads to significant improvement in patient's condition. In some cases at the early stages of the disease, it may result even in the full recovery. After the stem cell therapy, diabetes mellitus patients report normalization of immunological and haematological indices, reduced manifestations of micro- and macroangiopathy and trophic disturbances, restoration of workability. In case of treatment the disease progression is hindered, and periods of remission become 2–3 times longer. Severity and frequency of diabetes complications decrease. Life quality and average life expectancy increase. Indications for diabetes treatment with fetal stem cells.

Stem cell treatment of diabetes is indicated at all stages of the disease. It is, however, the most effective in the cases of:

- ►new-onset insulin-dependent diabetes mellitus;
- ►diabetes mellitus complicated by diabetic glomerulosclerosis, chronic renal failure (grade 1 and 2) and anemic syndrome;
- ►labile course of diabetes mellitus;
- ►diabetes mellitus associated with infection complications and immune deficiency;
- ►presence of resistant to treatment trophic ulcers of the soft tissues;
- ►secondary sulfanilamide resistance and the need for patients with diabetes mellitus type II to transfer to insulin therapy.

To cure type 1 diabetes, stem cell replacement needs to be more than simply a case of swapping insulin-producing cells from a healthy pancreas with those destroyed by diabetes in a diabetic patient. Numerous complications preclude this as a simple treatment. Islet cell transplants are one form of procedure that has proven effective. In type 1 diabetes, the body's immune system becomes programmed to attack the beta cells, so the patient must take immuno-suppressant drugs to prevent this happening. In the future, it may be possible to grow islet cells from patient's existing islet cells, however, a patient with type 1 diabetes would still need immune suppressants to prevent the cells being destroyed.

REFERENCES:

1. http://www.medicalnewstoday.com/info/diabetes/#.UJhTWDzqnf1
2. http://www.medicalnewstoday.com/releases/246471.php
3. http://www.medicalnewstoday.com/releases/240833.php.
4. http://www.network-weightdoctors.org/history-of-diabetes/diabetes-complications-diagram/
5. Michael DM, Christian TOSO, Emmanuel EB, James AMS. Are stem cells a cure for diabetes? Clinical Science 2010; 118: 87–97.
6. Tuch BE. Stem cells—a clinical update. Australian Family Physician,\ 2006; 35(9): 719–21.
7. Becker AJ, McCulloch EA, Till JE. Cytological demonstration of the clonal nature of spleen colonies derived from transplanted mouse marrow cells. Nature 1963; 197(4866): 452–454.
8. Siminovitch L, McCulloch EA, Till JE. The distribution of colony-forming cells among spleen colonies. Journal of Cellular and Comparative Physiology 1963; 62(3): 327–336.
9. http://www.nature.com/nrendo/journal/v6/n3/fig_tab/nrendo.2009.274_F2.html
10. http://kids.jdrf.org/index.cfm?page_id=109760
11. Singec I, Jandial R, Crain A, Nikkhah G, Snyder EY. The leading edge of stem cell therapeutics. Annu. Rev. Med. 2007; 58: 313-328.
12. Csaki C, Matis U, Mobasheri A, Ye H, Shakibaei M. Chondrogenesis, osteogenesis and adipogenesis of canine mesenchymal stem cells: a biochemical, morphological and ultra structural study. Histochem. Cell Biol. 2007; 128(6): 507–20.
13. https://en.wikipedia.org/wiki/Stem_cell
14. http://stemcelltherapy-india.blogspot.in/
15. http://www.medscape.com/viewarticle/776768
16. http://www.diabetes.co.uk/Diabetes-And-Stem-Cell-Research.html
17. Mehboob AH, Neil DT. Stem-cell therapy for diabetes mellitus. Lancet 2004; 364: 203–05.