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Curing Of Diabetes Mellitus by Stem Cell Therapy: A Review

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Abstract : *Diabetes, a common well known disease world wide. This is one type of disorder of metabolism. The main cause of diabetes is the malfunction of pancreatic beta cells, which maintain a significant role of body's glucose level concentration controlling. Several medications techniques were taken into account previously for the curing purpose of diabetes. But no effective and ultimate results were found. So, there is a demand for alternative therapeutic techniques. Due to increase in numbers of patients day by day worldwide shows an attitude to recent approach ,like insulin (exogenous). Due to lack of much numbers of pancreas donor, technique which is based on stem cell therapy has been taken into account. Stem cells have great poliferation characteristics which act as the mine of islets progenitor cells. Which can re synthesize the insulin. These cells exhibit sensitivity to glucose. There is a frequency around 415 million people suffer from this disease world wide. Beta cells are generally destroyed in type 1 and beta cell numbers are down by 40% to 60% in in type 2 diabetes. This article focus on current study on stem cell therapy for curing of diabetes mellitus.*
Keywords :*Beta-cells, Diabetes mellitus, Exogenous insulin, Hyperglycemia, Pluripotent stem cells.*

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I. INTRODUCTION

Diabetes Mellitus (DM) is a condition where hyperglycemia is caused by islets β-cell function deficiency (type I) and inadequate insulin secretion and/or the context of insulin resistance (type II) [1]. In type I DM is known as "insulin-dependendent diabetes mellitus"(IDDM)/ "juvenile diabetes". And type II DM is known as "non insulin-dependent diabetes mellitus"(NIDDM)/ "adult-onset diabetes". There is an increase in the levels of glucose in our blood during diabetes mellitus. The main symptoms of diabetes are, (i) frequent urination, (ii) increased thirst, and (iii) increased hunger. Many serious complications may arise if we left it untreated, such as (i) cardiovascular disease, (ii) diabetic kitoacidosis, (iii) stroke, (iv) kidney disease, (v) damage of the eyes, (vi) foot ulcer etc. Patients are unable to restore the normal blood glucose level, due to lack of insulin synthesizing pancreatic β. β-cells in the pancreatic islets of Langerhans are responsible for the production of insulin and much of the pathology of diabetes losses can be attributed to the loss of β-cell number and function [3,4]. For restore the function of pancreatic β-cell, recently developing stem cell study provides a great potential. Scientist are able to transmission embrayonic stem cells into beta cells in the laboratory. These stem cells has the potentiality to regenerated via division into mult-line cells. Hyper glycemic control can be control by inject insulin (exogenous). The fact is,exogenous insulin cannot maintain the optimum physiological level of glucose and is often accompanied by hypoglycemia [6]. Islet transplantation has some drawbacks,which can be avoided by stem cell therapy. Diabetes can be treated and controlled by dietary changes and oral medications. Of these, less than half of the patients are recommended for hemoglobin A1c (Hb A1c) level for therapeutic efficiency since exogenous insulin cannot provide the tight glycemic control exerted by pancreas-derived insulin [7]. Patients can give their own stem cells to be expanded and differentiated in vitro into islet producing cells. The autologous cells then can be injected back into the patients , thus get off possibilities and complications of graft rejection,and/or a requirement for and immune suppressive regimen. Recent studies on insulin-producing cells (IPCs) based on three sources, embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), and mesenchymal stem cells (MSCs), derived from a variety of adult tissues. iPSCs have the unique abilities of self-renewal and differentiation into many types of cell lineages. These are generated from somatic cells using various transcription factor [8]. Stem cells present in the pancreatic duct and islets,that have the ability to differentiate into the pancreatic exocrine and endocrine with number of pancreatic stem cells increase upon the destructive immune response. So, that pancreatic stem cells are used for the formation of functional endocrine cells in vitro condition. Pancreatic stem cells differentiating into endocrine cells have pancreatic duodenal homeobox- 1(PDX-1) and neurogenin 3. Hematopoietic adult bone marrow (BM),one type of adult stem cells, has the ability to transdifferentiate into the classical embryonic germ cell layers: ectoderm, mesoderm, and endoderm [9]. Hematopoietic stem cells (HSCs) mature to produce all the cells in the bloodline, while MSCs are involved in tissue regeneration and mature to produce various organs such as bone, cartilage,

heart, brain, and kidneys. Human fetal pancreatic cells also have the ability to differentiate into the insulin producing cells in vitro. Tests were conducted on human and several animals.

II. CURRENT MEDICATIONS

Insulin is currently use for curing both type of diabetes, but there are such drugs, which can be used, such as:

1) Metformin & it's combination with other drugs ,
2) Amylinomimetic drug (pramlintide) ,
3) Biguanides (i.e metformin-canagliflozin, metformin-dapagliflozin, metformin-empagliflozin, metformin-glipizide, metformin-gluburide, metformin-pioglitazone, metfoemin-repaglinide, metformin-rosiglitazone) ,
4) Sulphonylureas (i.e glimepiride, glimepiride-pioglitazone, glimepiride-rosiglitazone, gliclazide, glipizide, glipizide-metformin, tolbutamide, tolazamide, chlorpropamide) ,
5) Thiazolidinediones (i.e rosiglitazone, rosiglitazone-glimepiride, rosiglitazone-metformin, pioglitazone, pioglitazone-alogliptin, pioglitazone-glimepiride, pioglitazone-metformin) ,
6) Meglitinides (nateglinide, repaglinide, repaglinide-metformine) ,
7) Dopamine D_2 agonist (Bromocriptine) ,
8) Alpha-glucosidase inhibitors (acarbose, miglitol) ,
9) Glucagon-like peptides (i.e albiglutide, dulaglutide, exenatide, exenatide extended-release, liraglutide) ,
10) Sodium-glucose transporter 2 inhibitors (i.e dapagliflozin, dapagliflozin-metformin, canagliflozin, empagliflozin, empagliflozin-linagliptin) ,
11) DPP4 inhibitors (i.e alogliptin, alogliptin-metformin, alogliptin-pioglitazone, linagliptin, linagliptine-empagliflozin, linagliptine-metformin, sexagliptin, sexagliptin-metformin, sitagliptin, sitagliptin-metformin, sitagliptin & simvastatin) ,
12) Others drug ,such as: aspirin .

III. RESTRICTION OF TRADITIONAL TREATMENTS

Now a days complications of diabetes are not curable by the medicines. Due to,they do not giving sufficient controlling power on glucose level concentration in blood. We can transplant whole pancreas, because it was a workable treatment. But long term immuno-suppression and surgery like some serious issues are there. Also there was less availability of pancreas donor. Surgery was not very successful sometimes. Also daily insulin injection for serious patients turn into a phobia and can hamper the normal daily life. Also, over doses of insulin can also suddenly decrease the blood sugar level. Not only for the patient but also his/her relatives are also suffer from a serious bad situation which can also effect the society. Mainly, the price needed for the treatment of diabetes is high because of increase in number of diabetic patients day by day. So, there must be development and search for a new better therapeutic methods regarding diabetes treatment should be concern. Although diabetes can't be curable completely, it can only be control by proper medication and treatment methods and healthy dietary regulation & physical exercise.

IV. Properties Of Stem Cells

While describing the stem cells, two properties must be clarify, one is "Self-renewal" properties and another is "Potency".

1. Self-renewal Property

While hold over the uniform state, its the power to go through many cycles of division. There were two types of working mechanism, which clarify that the grouping of stem cells is maintained, they are (i) Stochastic differentiation, and (ii) Obligatory asymmetric replication. In obligatory asymmetric replication, one mother cells split into one identical stem cell to the original and another into a daughter cell, which is completely different from the original mother cell. In stochastic differentiation one mother stem cell produces two distinguished daughter cells and another goes to mitosis cell division to produce two stem cells, completely look like as original mother cell.

2. Potency

It is the property or capacity to differentiate the stem cells into a group of specialized cells, either pluripotent or totipotent. There are several types of potent stem cells, such as :(i) Totipotent (they can differentiate into extra-embryonic and embryonic cells), (ii) Pluripotent (they can differentiate into all type of cells), (iii) Multipotent (can differentiate cells which are closely related to each other) and (iv) Unipotent (it has the ability to produce only one type of stem cells).

V. SOURCES OF STEM CELLS

The collection of stem cells were made from different sources, such as-

(i) Bone marrow, (ii) Umbellical cord, (iii) Embryos, (iv) Blood cells, (v) Placenta, (vi) Teeth etc.

VI. DIFFERENT TYPES OF STEM CELLS

There are several types of stem cells, which can be implant for the treatment of diabetes. The major importance was given to collect these stem cells. Apart from this, these stem cells play an important role in the diabetic treatment.

1. Fetal Pancreatic Stem Cells

Over past few decay, major development had put over on fetal stem cells development and transplantation. This provide useful guideline for the synthesis of islet in vitro. Pancreatic stem cells was first used for the synthesis of insulin. Which was active in nature. They took pancreatic cells of fetus. And then they isolated the cells by the help of various markers (PDX1 & NGN3). Then the cells are put into culture media. After that they produced structures which are islets like. Then insulin was started to synthesis.

2. Induced Pluripotent Stem Cells

iPSC's is a novel resource of stem cell theraphy for Diabetes disease.Induced Pluripotent Stem Cells have the unique abilities of self-renewal and differentiation into many types of cell lineages. These are generated from somatic cells using various transcription factors. According to Yamanaka et al. The terminally differentiated cells could relapse back into pluripotent stemcells (iPS cells) by forcing the expression of small number of factors. The characteristic of IPSCs have showed a new way of success in designing patient's specific treatment from the patient's own somatic cell by the process of nuclear reprogramming with the help of factors. This type of cell theraphy reduces the possibility of immunologic rejection of embryonic cells though they are autologous . Furthermore, the formed iPS cells show limitless proliferative activity and form teratomas upon transplantation [10]. They also carry epigenetic memory characteristic of the somatic cell of their origin. This favourdifferentiation along lineages related to the donor cells [11]. The possibility ofgenerating Insulin-secreting isletlike clusters from iPS cells derived from human skin fibroblasts was first reported by Tateishi et al.[12]. But in a recent report, human iPS cells derived from both fetal and adult human tissues were differentiated in vitro into pancreas-committed cells. And at the end of in vitro differentiation, approximately 5 % of cells became insulin positive. But when it is transplanted into immunodeficient mice model, the transplanted cells lost their insulin secretion capacity in response to glucose stimulation [13].Hence it is clear that the utilization of iPS cells to form IPCs requires additional improvement and optimization before their application can be clinically significant.

3. Mesenchymal Stem Cells

The mesenchymal stromal cells are basically heterogeneous, multipotent stromal population of non-haematopoietic progenitor cells with the ability to discriminate into multiple mesenchymal lineages like bone, fat and cartilage. MSCs are derived from bone marrow stroma .These are considered as the most hopeful therapeutic tool for tissue regeneration and repair. The International Society for Cellular Therapy proposed three criterion to define MSCs [14]. First, MSCs must be plastic adherent when maintained in standard culture conditions using tissue culture flasks. Second, 95 %of the MSC population must express CD105, CD73, and CD90 as measured by flow cytometry. In addition, these cells must lack expression (≤2 %) of CD45, CD34, CD14, and HLA class II. Third, the cells must be able to make a distinction into osteoblasts,adipocytes , and chondrocytes under standard culture in vitro differentiating conditions .MSCs can be derived from a variety of human tissues and have a high capacity to replicate. They are easily cultivated and expanded remarkably and can maintain their multi lineage potential following prolonged culture conditions [15]. Besides they are nonteratogenic and they have pro-angiogenic , anti inflammatory& immunomodulatory characteristics. All of these reasons make them an excellent tool for use in regenerative medicine, including in potential therapeutic use for DM. MSCs are easily procurable from virtually every tissue[16].According to an survey the maximum number of MSCs is found in neonates & it is reduced to its one half at the age of 80[17]. In diabetic NOD mice, it is shown that the injection of MSC has the capability to reduce the diabetogenicT cells to penetrate pancreatic beta cell islets and thus preventing the β-cell destruction [18]. The mutual action of MSC's in co-transplantation with pancreatic islets resulting in the amended graft morphology and improved revascularization representing that the probable trophic factors secreted by MSCs are helpful in islet engraftment [19]. MSCs were able to distinguish pancreatic insulin producing cells in STZT1DManimal models, secreting insulin and relief, diabetic complication. These insulin producing cells articulate multiple genes such as duodenal home box 1 insulin, and glucagon and were able to secreate insulin that responsible for decrease glucose level and hence ameliorate diabetes in STZ- nude mice [20].Some trophic factors, such as vascular endothelial growth factor [21], ciliary neurotropic factor,Von Willebrand factor [22], and Il-6 , can be released by MSCs and have the ability to extend islets' life.

4. Embryonic Stem Cells of Human

Along with Mesenchymal stem cells it has been studied that Embryonic stem cell (ESCs) can also be used to normalize blood glucose level in streptozotocin-induced diabetic mice. Human embryonic cell origin have the capability for quick replication and the ability to separate into cells of all three germ layers (trilineage differentiation). These two features make them an attractive resource for the generation of IPCs.The ESCS

separation of mouse using five step protocols was successfully reported by Lumenlsky et al. latter it was modified by Segev et al by introducing a step of suspension culture at the end of the differentiation protocol. A group of scientist, Baetge &colleagues provided an evidence of principle and sophisticated a protocol for the efficient differentiation of human ESCs into insulin-secreting cells and then directing the cells through successive stages towards determinant endoderm, gut tube endoderm, pancreatic endoderm & pancreatic endocrine lineage. The main tactic of that group is to transplant the resultant pancreatic progenitors within an encapsulation device to resist immuno rejection. With the help of undifferentiated human ESCs line,successful generation of putative IPCs was reported by Pagliuca et al[23]. Inspite of having advantages this type of cell theraphy has two drawbacks such as their teratogenicity & immunogenicity.

VII. CONCLUSION

There has a lot of future opportunity for the use of stem cells in the curing purposes of diabetes. This article has show many of the main role of stem cells in diabetes therapy. Self renewal property and potency make it more acute therapeutic. All types of these stem cells has the ability to reproduce the pancreatic beta cells. It must be a better way to avoid daily insulin injection. Although , it's now in development stage, for further better study.There is a hope for a diabetes free world in future, by the help of stem cells.

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