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Stem Cell Therapy in Diabetes Mellitus

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Abstract

Diabetes mellitus is one of the world's oldest known diseases characterized by high blood glucose level. Cases of diabetes and its consequences are rapidly increasing across the globe. Numbers of conventional therapies including exogenous insulin administration, drugs, lifestyle changes do not provide curative treatment for diabetes. With a aim to restore the endogenous production of insulin rather than the conventional insulin injection, transplantation of pancreas/islet cells can be a novel replacement of these conventional therapies. For success of transplantation major obstacle is to obtain large number of pancreas and islet cell donor, besides immune-rejection. In addition, survival, proliferation, and functionality of isolated islets following transplantation is also an unresolved complication. These problems can be overcome by regeneration of beta cells from stem cells. High capacity of differentiation of stem cells can be a game changer in the field of regenerative medicine and can provide a curative future for diabetes.

Introduction

Diabetes mellitus (DM) is characterized by hyperglycaemia resulting from defects in insulin secretion, insulin action or both (Mishra et al. 2010). According to WHO report published in November 2021, the number of people with diabetes rose from 108 million in 1980 to 422 million in 2014. Prevalence has been rising more rapidly in low- and middle-income countries. In 2019, diabetes was the ninth leading cause of death with an estimated 1.5 million deaths directly caused by diabetes. In addition, diabetes is the No. 1 cause of kidney failure, lower-limb amputations, and adult blindness (cdc.gov).

On the basis of pathogenesis, it is mainly categorized as follow- i) Type I DM- It occur because of an autoimmune destruction of beta cells of pancreas, leading to decrease or absence of insulin

secretion, necessitating patient to take exogenous insulin. This is the reason for it being also known as Insulin Dependent DM (IDDM). Approximately 5-10% of the people have type 1 diabetes and its symptoms often develop quickly. It's usually diagnosed in children, teens, and young adults. ii) Type II DM – In this type, insulin production is normal but the insulin resistance of the target cells develops which results hyperglycaemia, it is also known as Insulin Independent DM (IIDM). It develops over many years and is usually diagnosed in adults. About 90-95% of people with diabetes have type 2. iii) Gestational DM – It appears during the second trimester of gestation causing high blood glucose level and disappears after the birth of the baby (Mishra et al., 2010). Diabetes also occurs in animals with overall incidence of approximately 0.5-1%. Overt diabetes is rare in horses, cattle, and sheep. Isolated cases of diabetes have been reported in mules, ferrets, pigs, newts, buffalos, monkeys and fish. (Veterinary Pharmacology and Therapeutics by Riviere and Papich, 2017)

Treatment of diabetes

1) Drugs/Medicines: Patient suffering from diabetes have to take either lifetime exogenous insulin (in type 1) or drugs for a longer period of time, in addition to lifestyle changes which makes it mental and economic burden. Different kinds of diabetes medicines with their site of action and associated side effects are represented in Figure 1 and table 1, respectively. These medicines are most often used to treat type 2 diabetes. Diabetes medicines do not act the same in each person. These medicines can sometimes cause side effects. The side effects will depend on your body and the type of medicine you are taking. In addition, diabetic complications like retinopathy, neuropathy, nephropathy (microvascular complications) and cardiomyopathy, diabetic wound, diabetic bone (macrovascular complications) makes it more difficult to treat and life threatening.

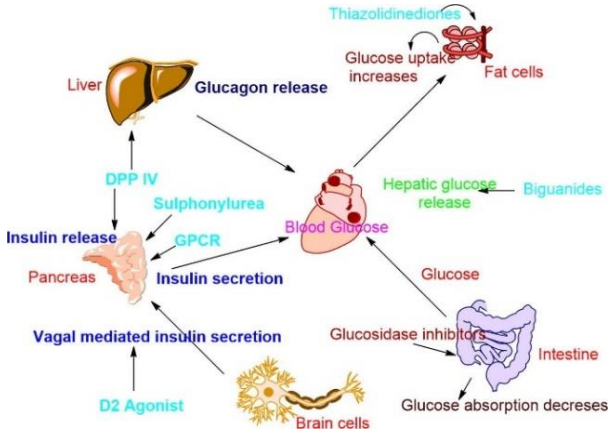

Figure 1: Site of action of different class of drugs associated with changes on glucose level Taken from: Dowarah and Singh, 2020

S/N	Drug class	Example of drugs	Adverse effects
1	Insulin and analogues	Regular Insulin	Hypoglycemia, Weight gain, Insulin allergy, Lipodystrophy at injection sites
2	Sulphonylureas	Glibenclamide	Hypoglycaemia, Weight gain, Cardiovascular risk, rash, Cholestatic jaundice, Bone marrow damage, Photosensitivity
3	Meglitinides	Repaglinide	Hypoglycemia, Sensitivity reactions
4	Biguanides	Metformin	Gastrointestinal effects, Lactic acidosis
5	GLP-1 agonists	Exenatide	Gastrointestinal effects, Pancreatitis, risks for cancer and cardiovascular events
6	DPP-4 inhibitors	Saxagliptin	Pancreatitis, risk for cancer, acute hepatitis and kidney impairment
7	Thiazolidinedions	Pioglitazone	Hepatitis, Cardiovascular risk, Bladder cancer, Water retention and weight gain
8	Dual PPAR agonists	Saroglitazar	Gastritis, asthenia and pyrexia
9	Alpha-glucosidase inhibitors	Acarbose	Gastrointestinal effects, Hepatitis,
10	Amylin analogues	Pramlintide	Hypoglycemia, Allergy
11	SGLT 2 inhibitors	Canagliflozin	Glycosuria, Cardiovascular concern

Table 1. Conventional antidiabetic drugs and their major adverse effects (Taken from: Osadebe et al., 2014.

2) Other treatment options: These include weight-loss (bariatric) surgery for certain people with type 1 or type 2 diabetes and obesity, or pancreatic islet transplantation for some people with type 1 diabetes (niddk.nih.gov), and stem cell therapy. Although response to weight loss surgery vary by patient, type of weight-loss surgery, and the amount of weight the person lost, researchers are studying whether weight-loss surgery can help to control blood glucose levels in people with type 1 diabetes who have obesity (Vilarrasa et al., 2021). On the other hand, islet transplantation or stem cell therapy involves induction of insulin producing cells (pancreatic beta cells). In islet transplantation, islets from a deceased donor are infused (dripped) into a vein in the liver. If the transplant is successful, the islets lodge in the liver and start to produce insulin. Limitations like immune-rejection, non-functioning of transplanted islet, need for at least two infusions in most people vs. limited pancreatic availability, deterioration of islet function over time, masks the potential of this therapy on account of which still it is considered an experimental procedure and is not an approved treatment (citisletstudy.org). Considering the aforesaid limitations of various therapeutic approaches, stem cells nurtured *in vitro, ex vivo or in vivo* micro environment on account of their differentiation potential can lead to regeneration of large number of the cells required for therapy of diabetes (Mishra et al., 2010).

Stem cells and their role in treatment of Diabetes Mellitus

Stem cells are self- renewing, unspecialized cells that give rise to multiple specialized cells through process of differentiation (Mishra et al. 2010). On the basis of their origin stem cells are classified as follow-: Embryonic stem cell, Fetal stem cell, Perinatal stem cell, adult stem cell and IPSc (induced pluripotent stem cells) (Barzegar et al. 2019). Regenration of beta cells from different sources like HSC (Haematopoetic stem cells), MSC (Mesenchymal stem cells), ESC, Duct cells, micro RNAs etc. are shown in figure 2.

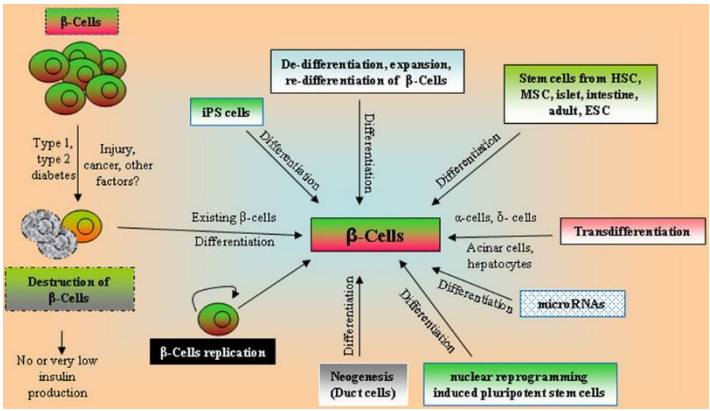

Figure 2. Possible sources of beta-cells for cell replacement therapy (Taken from Mishra et al., 2010).

Role of stem cells in treatment of DM

Potential of stem cells to differentiate into other cell types, initially involved research on human embryonic stem cells taken from embryos of terminated pregnancies. Reduction in HbA1c and fasting blood glucose level in patients with a type 2 diabetes mellitus (T2DM) was reported after administration of autologous bone marrow-derived mesenchymal stem cells (Nguyen et al., 2021). Likewise, in type 1 Diabetes Mellitus for example, increased C-peptide levels, indicative of beta cell function and reduction in associated risk of microvascular complication and insulin independence following autologous nonmyeloablative hematopoietic stem cell transplantation has also been reported (Couri et al., 2009). Continuing on this path, various experiments viz., induction of β-cell proliferation in Streptozotocin induced diabetic mice by transplantation of adipose-derived mesenchymal stem cells (Sun et al., 2017); therapeutic potential of human embryonic stem cells in type 2 diabetes mellitus in humans (Shroff, 2016), highlighted the role of stem cell in diabetes. Highlighting further, recently in June 2022, VX-880, an investigational stem cell-derived, fully differentiated pancreatic islet cell replacement therapy developed by Vertex Pharmaceuticals for people with T1D showed promising result with improvements in glycemic control and reductions in exogenous insulin requirements (investors.vrtx.com).

Conclusion

In the new era of regenerative medicine stem cells are key elements. There are number of diseases which do not have a permanent solution, diabetes is one of them. Benefits of stem cell therapy in reversal of diabetes in greatly acknowledged, now focus is on transforming human stem cells into pancreatic progenitor cells, rather further transform these into fully differentiated islet cells. Use of pancreatic progenitor cells in diabetes treatment is in fourth and fifth trials, when compared to fully differentiated islet cells. Fully differentiated cells although offers better control of the cell dosage that people receive, use of progenitors introduces extra layers of variability and uncertainty, as well as months of waiting for functional cells to emerge. Although stem cells have enormous potential of differentiation, problem associated with protection of these cells immune system, improving rate of differentiation in a controlled microenvironment, and ethical issues are some of the concerns. In nutshell, just like other therapies there is also pro and cons of stem cell therapy, so, it is very important to understand benefit vs risk ratio before their application.

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