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Review Article

Role of Stem Cells in the Management of Type-I Diabetes Mellitus

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ABSTRACT

The paper aims to accent Type-1 DM along with its etiology, pathophysiology, and treatment in this review. Diabetes is considered the chronic ailment of hypoglycemia ensuing from the duo of the dearth of insulin action and secretion of insulin considered as both. Moreover, Type-1 is a result of autoimmune of the cells of islets of the pancreas. The confrontation to the insulin or secretion of insulin lacking due to changes in living standards, habit change, dearth of exercise along with aging also, but one of the most relevant and prevalent reasons is a lifestyle change and also change in food habits along with the stress of the day-to-day life. Stem cell therapy is an expensive treatment and obtaining stem cells also is difficult due to ethical issues and availability is also less. Presently accessible ailment for type-1 is insulin supply therapy but it is also associated with many hitches. Advanced replacements like islets have demonstrated fruitful results in reinstating glucose levels. Moreover, in severe type 1-DMM and it has been delimited due to its high cost, not economic process, shortfall of donors, etc. Replacement of beta-like cells that are obtained from differentiation of human Pluripotent Stem Cells (hPSCs) also exhibited results with flying colors and gained the spotlight, but in stem cell therapy getting beta cells along with complete insulin secretion is decisive.

Keywords: Diabetes Mellitus, Stem cells, Hyperglycemia.

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INTRODUCTION

Diabetes Type-1 is considered an autoimmune disease caused by T cells, along with the everlasting devastation of beta cells, in Type-1 Diabetes Mellitus (T1DM) patients it has been observed that it causes retinopathy, nephropathy and neuropathy. Insulin is one of the unsurpassed therapies, whereas in T1DM insulin deficit has been noted, by the usage of existing pens, and syringes blood glucose may decline but not for over some time. Transplantation of the pancreas and islets have been beneficial, but it didn't emerge as an effective approach due to the lack of donors. In type-1 DM ruining of beta cells have spotted due to immune response, and autoantigens like Glutamic Acid Decarboxylase (GAD), insulin, and IA-2 have been found, $CD8^+$ T cells, $CD4^+$ along with them macrophages, also natural killer cells, dendritic cells have extended their contribution in beta cells destruction. In autoimmune disease regulatory T cells (T reg) have a major involvement in developing T1DM they were found to vary in the function and number in the pancreas.

The Sum of IFNγ regulatory T cell production was found to be suggestively less in T1DM patients' peripheral blood. Beta cell demise is due to the production of Reactive Oxygen Species (ROS) which is produced by the differentiation of $CD8^+$ cells produced by macrophages and followed by the production of TNF and IL-18. For example, environmental aspects strappingly have a role in the progression of T1DM. The abnormal intrusion of T cells destroys the beta cells by entering into the islets as they will not identify antigen as the self-antigen.[1] Found to be highly genetic in humans, along with the autoantibodies also found at the onset of diabetes in peripheral blood, an upsurge in CD4+ proliferation was reported in the presence of GAD in islets and the brain of humans. Induced Pluripotent Stem cells (iPS), and Embryonic Stem Cells (ESC) can differentiate into beta cells. ESC is harvested from blastocysts, and they develop into and can differentiate into endoderm, mesoderm, and ectoderm cells.

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Upon transplantation, the diabetic mice developed into insulin-releasing cells, and fascinatingly they released insulin against the response to glucose stimuli to stabilize glucose levels in the blood. iPS obtained from adult mouse embryonic and cultures of fibroblast having namely four factors i.e., Klf4, Sox2, Oct3/4, and, c-Myc. Normal T and B-cells are found in Bone Marrow (BM) cells and also, and they were tolerant to both donor and acceptor, based upon these results, suggest that Allogenic Bone Marrow Transplantation (ABMT) may avert the demise of beta cells and also provide aid in self-tolerance restoration. Even beta cell revival promoted by BMT, MCSs are not only extracted from BM they can also be obtained from cord blood and adipose tissue, they induce T-reg cells, in the pancreas, which were suppressed by the proliferation of beta cells and they give assistance in to overcome from the autoimmune pathophysiology which is inherited in T1DM.

Upon transplanting allogenic amniotic stem cells which are rich in $CD34^+$ cells to a T1DM young patient, for 36 months follow-up it has been found to be very promising results have come out, and also hyperglycemia condition has been found to be improved moreover without insulin therapy. Diabetes is one of the main leading causes of death and it stands in seventh place in the USA. It has been considered by its value of high blood glucose levels in fasting conditions, its value determined by amassing the blood sample from the patient who has been fasting.[2] Some recent findings have found the interplay in cells of the pancreas and its role in proper reaction to glucose stimulus, in 3D cells they have exhibited better glucose level change than in the GSIS test. Pancreatic islets *in vitro* models developed where the microenvironment for cells is conserved very well.[3] By mixing diverse cells type amongst the others, followed by suspension in protein hydrogels which forms a spatial tissue system, and in this kind of model, they interact with the gels and cells. While working with pancreatic islets, much more attention is paid, because, micro vascularization also plays a vital role and the pancreas must be serene with various endocrine cells, which is considered to be one of the decisive for homeostasis of glucose. Reproduction of perfect islets artificially and even generating mimicking microenvironment of islets is not sufficient to reach the expected and promising results for T1DM and the replacement of islets of the pancreas is at still in crossroads due to their flawed transplantation.

To produce an expected environment for islets by utilizing vasculature and extracellular, 3D printing has got moonlight as a solution for obstacles, and the advantage is it makes bioprinting of cells that are obtained from the cell cultures. Upon optimizing aspects and obstacles an intent bionic organ with functionality can be obtained, it depends upon the right assortment method for bioprinting. At present, there are four methods available for bioprinting, laser, inkjet, micro-extrusion, and Stereolithography (SLA). Among them, the most commonly used method in tissue engineering is SLA and the micro-extrusion method. More aspects that should be thoroughly evaluated are the bioprinting condition, bio-ink, printing speed, pressure, and cross-linking method. As of now, no more reports have been published regarding the 3D bioprinting application for T1DM. In the first attempt, they succeeded in printing the 3D islets of rats, mice, and humans using alginate-based bio-inks. Upon printing islets artificially, the morphology and viability of cells didn't change and they remained intact. But whereas in the case of rat's impact of bioprinting on cell morphology, functional ability, and viability was too small.

In 2019 3D pancreas bionic was printed with the help of vasculature using pancreatic islets, endothelial cells, and extracellular matrix with bio-ink of dimension 3X3 diameter, and 5X5 cm^3, which encompassed six lakhs equivalent islets and produced insulin. In diabetes, there are two types i.e., Type-1 and Type-2. Whereas in the first type, in pancreas beta cells have no ability to produce insulin and this is found in youngsters (Under 18 years), and about 75% of them have been identified with this type. Likewise in another type, where glucose is not permissible into beta cells in the pancreas which is essential for the production of energy for the body, moreover this is found in lethargic people and patients with more obesity, and with a family history of DM. The types of diabetes are given in Figure 1.

Usually, diabetes develops very quickly and these symptoms won't mimic or point to any other specific disorder or disease state it's called an insidious onset. Nevertheless, the symptoms develop very swiftly in the case of the first type, and the second type is considered to be more insidious, the confirmation of diabetes is confirmed only by the accomplishment of some medical check-ups. Polyphagia is a kind of symptom of diabetes which means extreme hunger feeling, this condition is caused due to carbohydrates, cellular protein, fat exhaustion, and cell starvation. Polydipsia means dehydration occurs intracellularly which is leading to an upsurge of thirstiness, followed by intensification of glucose levels in the blood. From the thirst center situated at the hypothalamic region. It's considered the initial symptom of the second type of diabetes often it is not detected at the initial stages specifically in individuals with regular increase in blood glucose levels. Polyuria is also a symptom of DM where surplus urination has been seen observed. Since glucose is a small molecule and osmotically active. The upsurge in glucose levels should be filtered from the kidney (Glomeruli part) and excreted which leads to a condition called glycosuria along with the loss of water with urine. The complications of diabetes are depicted in the Figure 2.

EMBRYONIC STEM CELLS (ESM)

After finishing of developmental stage i.e., the eighth stage, totipotency of the blastomeres losses rapidly as they are differentiating into two lineages viz Trophectoderm (TE) and Inner Cell Mass (ICM). TE function is predefined they develop

into the extraembryonic structure. ICM has encompassed with cells and they will emerge as the fetus. At the blastocyst stage the ESM they are confined in the ICM. They are pluripotent in nature and have the ability to discern into endoderm, mesoderm, and ectoderm. In *in vivo* conditions, pluripotent cells swiftly differentiate into fetus, and development continues. A group of scientists Martin and Evans were successful in isolating embryonic stem cells from the inner cell mass thru the mouse. Dated, 1998 scientists were able to derive embryonic stem cells from humans from the embryos produced from *in vitro* Fertilization (IVF). After the identification of stem cells, they have received fascinating concerns from nuke and corners of the world and many research and trials on humans were conducted and are ongoing also because of their fruitful outcome in the field of tissue engineering. They can be cultured and sustained by the regulation of epigenetic regulators and transcriptional activity, these will be supporting the pluripotency.[4]

Moreover, they own alkaline phosphatase enzymatic activity and they are expressing the gene which downregulates during the differentiation like NANOG and OCT4. If there is any change seen in the culture conditions cells begin to differentiate very speedily, actually it means the main challenge in utilizing, handling, and working on tissue engineering using stem cells is difficult because of directing the differentiation of them into anticipated cell types. One of the principal problems of ESC utilization in the clinical aspects or application is ethics because ESCs are obtained by extinguishing the embryo which has led to the stoppage of the usage of ESC and they are legally allowed in very rare cases. But they are permitted in treatments like personalized by the production of embryos autologous method by using therapeutic cloning, which means by using *de novo* the nuclei of the differentiated cells are transformed into de-nucleated oocytes, during this phenomenon reprogramming of chromoplast takes place and embryonic formation takes places. By this method,

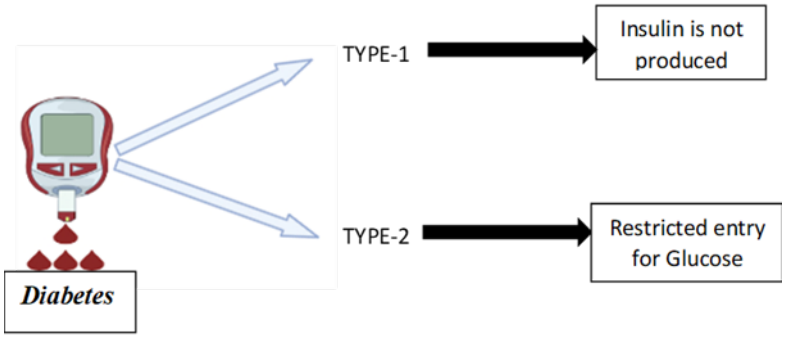

Figure 1: Types of diabetes.

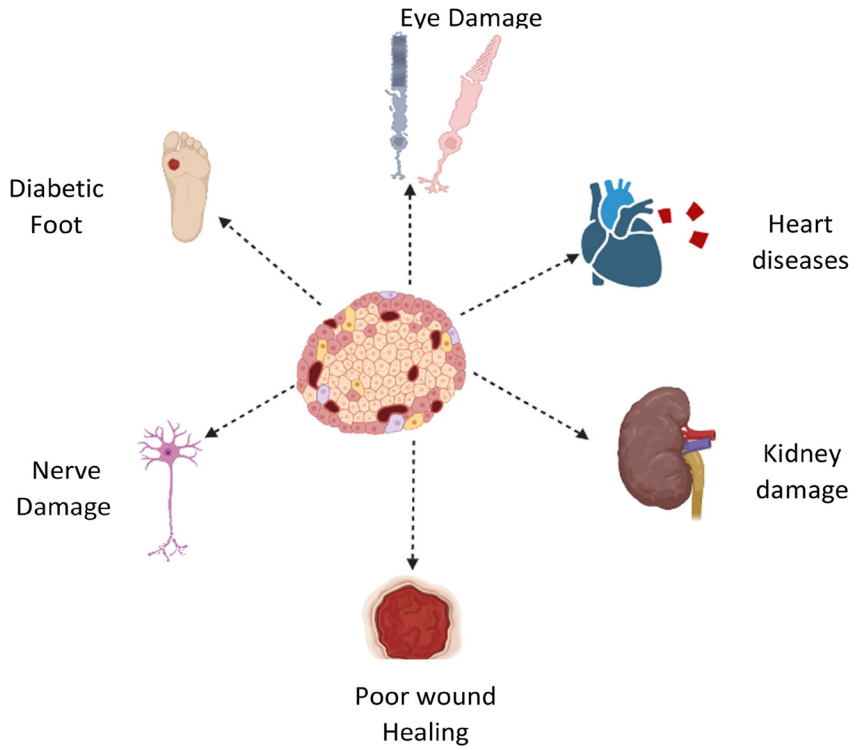

Figure 2: Complication of diabetes.

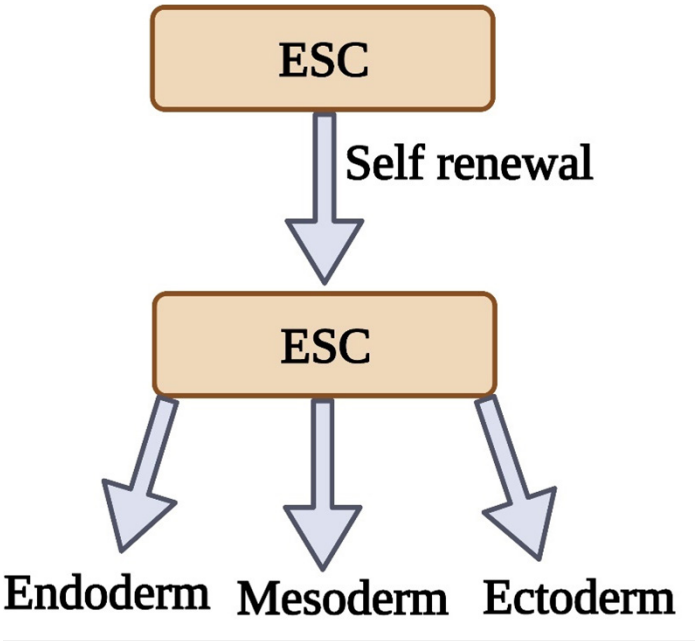

Figure 3: Stem cells property.

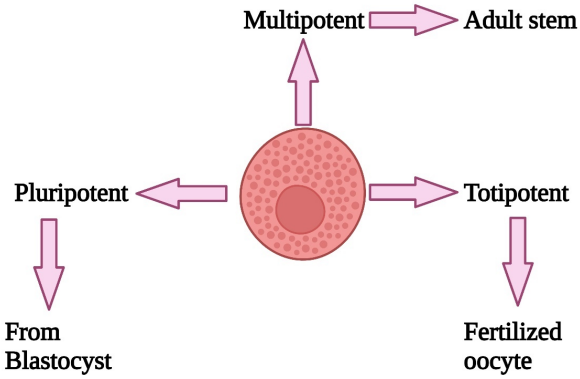

Figure 4: Types of stem cell.

development can be stopped at the desired point like they are obstructed in the blastocyst stage, and from here ESCs are gained. These techniques are considered as potential but still, the ethical problem remains the same. The stem cells property is given in Figure 3.

Overcoming ethical issues upon the usage of ESCs the induced Pluripotent Stem Cells (iPSC) come into the light. Takahashi and Yamanaka exhibited similar properties to the stem cells which have been derived by fibroblast of mice and also parallelly introducing OCT4, SOX2, NANOG, and LIN28 and thereby coined them as iPSCs. The next move was, they introduced the same genes into the fibroblast obtained from the humans and they were successful in engendering the iPSC of humans, later also evolved iPSCs even also from neurons and lymphocytes. The imperative question regarding iPSCs was they the same or unlike from ESCs if they are different in what way, they evolved to be different in most of the ways i.e., in the way of expression of genes, epigenetic memory of donor cells, and DNA methylation, at last, it was concluded that the difference is due to the culture conditions and induction way and it's tough to differentiate between ESC and iPSC. Stem cells are one of the supreme findings in this new millennium to treat disorders or diseases, there is still lots of research and work going on stem cells for their effective use in treating various disorders which could be a boon for mankind.

Believed that stem cells are one of the untouched works in the present century which can be used to treat many diseases and disorders also because of their regeneration properties. Stem cells are found all over the body and can grow into cells with specialized functions. Cells generate offspring, which can be formed into specialized cells or stem cells.[5] Stem cells maintain their population themselves, the division of each of them leads to the addition of another stem cell, and their number will remain stagnant if the symmetrical division is taking place. Stem cell inhabitants are present in fewer numbers in the whole body and they are undifferentiated moreover they don't have focused functions when they have given rise. They are found in many organs and tissues, but their property remains unidentified, whereas in bone marrow their inhabitants have been found with rekindling property and with well-defined differential potential. The types of stem cells are given in Figure 4.[3]

CONCLUSION

Diabetes Type-1 is considered as the one of the autoimmune diseases, which is characterized by an utter deficiency of insulin secretions. The present ailment for this condition is insulin administration from an external source. But insulin therapy also has many complications which are considered to be devastating, i.e., for instance, the patient might fail to take the supplement in time which will lead to the development of immediate complications like diabetic ketoacidosis. In the 21st century, there are alternative ailments for even T1-DM i.e., researchers have designed therapies like immunotherapy, stem cell, and islet replacement, for this condition. Amongst, stem cell therapy has gained a wide range of moonlight in treating T1-DM, and it's also not free of problems and obstacles it's also having hindrances like generating fully matured beta cells for secretion is still a challenging phenomenon for researchers. The first and foremost thing is to achieve an unchanged condition of nutrition, along with the microenvironment surrounding the development process and a few molecular mechanisms are also involved in beta cell maturation. Development of intact functioning of mitochondria should be achieved in SC-beta cells, in upcoming years for engendering the fully functional matured beta cells. Lastly, the compounds/ molecules that are very important for the maturation of beta cells need to be identified (Functional maturation of immune beta cells).

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

DM: Diabetes mellitus; **hPSC:** Human pluripotent stem cell; **T1DM:** Type-1 diabetes mellitus; **GAD:** Glutamic acid decarboxylase; **iPSC:** Induced pluripotent stem cell; **ESC:** Embryonic stem cells; **BM:** Bone marrow; **ABMT:** Allogenic bone marrow transplantation; **SLA:** Stereolithography; **TE:** Trophectoderm; **ICM:** Inner cells mass; **IVF:** *in vitro* fertilization; **IFN:** Interferons.

SUMMARY

Type-I DM is one of the most common autoimmune diseases occurs among general publics. The main risk factors associated with type- I DM are lifestyle modification, stress, imbalanced work life and improper food diet. Type- I Diabetes mellitus cannot be cured but it can manage with Pharmacological and Non-Pharmacological therapies. In recent days advancement in the stem cell therapy has gained attention and seen fruitful results, because of its self-regeneration property. Still, research is going on the usage and development of stem cells. Stem cells are considered to be an expensive therapy due to ethical issues obtaining stem cells is very difficult. The alternative methods have evolved by the researcher for the usage of stem cells. Replacing the beta cells which are derived from human pluripotent stem cells which have gained attention and get fully functioning stems with insulin secretion properties is difficult.

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