IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Review Article
November 2023 Vol.:28, Issue:4

Unveiling the Potential of Stem Cell Therapy in Diabetes Mellitus Management

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ISSN 2349-7203
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Submitted: 22 October 2023
Accepted: 27 October 2023
Published: 30 November 2023

Keywords: diabetes mellitus, stem cell therapy, embryonic stem cells, mesenchymal stem cells, clinical trials

ABSTRACT

Diabetes mellitus affects millions of people worldwide and is associated with serious complications that affect practically all physiological systems. Diabetes Mellitus is defined as a metabolic disorder characterized by elevated levels of blood glucose. Because of how important this worldwide health issue is, there is a lot of study being done on alternative medicines and prospective remedies. Diabetes was once treated with exogenous insulin infusion and pancreatic islet transplants. Long-term hyperglycemia caused by diabetes can have serious effects, including damage to the brain system and blood vessels, issues with vision, cardiovascular disease, and infections. Researchers are looking into potential treatments for diabetes because of the severe problems and significant expenditures that are linked with it. Stem cell therapy for diabetes is currently a major area of research because of the multiple disadvantages of other treatment options. The most recent research on stem cell therapy for diabetes is described in this review. Numerous studies on animals have used different stem cell types, such as mesenchymal stem cells and embryonic stem cells. The results and limits of animal research have also been supported by a number of clinical trials. Overall, stem cell therapy may be superior to insulin injections and other treatments; current clinical trials suggest that this therapy may soon be a real alternative for diabetics.

INTRODUCTION:

One of the most pressing worldwide health concerns of the twenty-first century is Diabetes Mellitus. Diabetes Mellitus is defined as a metabolic disorder characterized by elevated levels of blood glucose. From 171 million in 2000 to 366 million in 2030, there will be an increase in the number of people with diabetes. Type 1 diabetes mellitus is due to the autoimmune destruction of insulin-producing beta cells of the pancreas causing either partial or complete insulin deficiency and this accounts for about 10%. The autoimmune destruction is due to genetic and environmental factors. Type 2 diabetes mellitus is due to beta cell dysfunction or insulin resistance. Exogenous insulin and hypoglycemic medications reduce hyperglycemia, but they are unable to prevent problems associated with diabetes mellitus or maintain the ideal physiological level of glucose, which can result in hypoglycemia[1]. Maintaining control over insulin administration is challenging since an excessive amount of insulin can cause hypoglycemia and, in severe cases, coma, while an insufficient amount of insulin can cause harmful hyperglycemia. Long-term hyperglycemia caused by diabetes can have serious effects, including damage to the brain system and blood vessels, issues with vision, cardiovascular disease, and infections. Researchers are looking into potential treatments for diabetes because of the severe problems and significant expenditures that are linked with it[2].

Alternative treatments include pancreatic and islet cell transplants, stem cell therapy, and anti-CD3 monoclonal antibodies for both types of diabetes[2]. When an appropriate donor is found, donor islet cells containing beta cells are collected and injected into the patient's hepatic portal vein. Having a small donor pool makes this challenging. Islet cell and pancreas transplantation has a low success rate, a shortage of donors, requires lifetime immunosuppressant treatment, and increases the risk of infection and cancer[5]. About 5% of patients were insulin-independent after Anti CD3 monoclonal antibody therapy[1].

Alternative beta cell sources include stem cells, porcine cells, and growth agents that promote beta cell multiplication. A stem cell is an unspecialized cell with the ability to self-renew and the potential to differentiate into a variety of specialized cells[4]. Stem cells have the capacity for regeneration, multilineage differentiation, and immunomodulation[1]. According to in vitro research, stem cells multiply in cell culture under favorable conditions while also retaining their pluripotency[4]. The ineffective insulin-producing cells of the pancreas can be replaced by stem cells since they have the capacity to regenerate damaged body cells[2]. Human embryonic stem cells (hESC), pluripotent stem cells, and adult/mature stem cells (umbilical

cord blood stem cells, peripheral blood mononuclear cells, and bone marrow mononuclear cells) are among the various types of stem cells[1].

Because stem cells have the ability to heal a wide range of crippling & degenerative illnesses, their use in the treatment of damaged tissue in diabetes has grown significantly. The body's specialized cell lineages can develop from stem cells, which are unspecialized cells with the ability to continuously self-renew. Human embryonic stem cells (hESC) and adult stem cells are two different kinds of stem cells. All of the cells in the human body, with the exception of additional embryonic tissue like the placenta, are produced by the plasticity of pluripotent embryonic stem cells (ESCs)[5].

Adult bone marrow stem cells can differentiate into hepatocytes, cardiomyocytes, brain cells, and other types of cells due to the availability of adult multipotent stem cells in humans and their capacity to preserve plasticity. Despite the success in converting and differentiating stem cells into cells that produce insulin, the success rate is very varied, and this approach is also contentious. However, the outcomes of recent research have shown encouraging results in the production of beta-like cells from hESCs[6].

Embryonic stem cells are isolated from the preimplantation embryo and have the ability to differentiate into any type of cell with 3 germ layers. Various techniques that imitate the signaling system during the formation of the embryonic pancreas have been developed in laboratories in order to differentiate embryonic stem cells into beta cells. When necessary, growth and inhibitory agents are added to simulate the process that takes place in vivo[7]. Similar techniques can also be employed using adult stem cells to create beta cells, and this method is more practical and less contentious[8].

Stem cells have been used in numerous clinical and pre-clinical research for diabetes. The presence of C peptide is tested in these patients in order to evaluate the effectiveness of treatment. Because it is produced as a byproduct of insulin release, c-peptide is a sign that beta cells that have differentiated from stem cells are producing insulin effectively[9]. For a period of three months, hemoglobin A1c is used to measure the average level of blood glucose, and lower results signify better glucose control[10].

The ability of ESCs to self-renew and their pluripotent ability to develop into any kind of embryonic cell under in vivo and in vitro settings are among its crucial properties. The stem cell keeps its characteristics during proliferation in cell culture, allowing for limitless growth without sacrificing its ability to differentiate. ESCs are superior to other cells due to this

characteristic, which is necessary for therapeutic uses when huge cell numbers are needed. Therefore, certain procedures must be followed along with signaling molecules and transcription factors to enable undifferentiated progenitors to differentiate into pancreatic endocrine cells in order to produce insulin-producing beta-cells.

How to produce terminally developed pancreatic beta-cells is the key query. Numerous ways for the neogenesis of beta-Cells employing ESCs, adult pancreatic stem cells, or other nonpancreatic cell types have been demonstrated over years of study. To comprehend the differentiation into islet hormone-secreting cells, several cell types are researched alongside ESCs, bone marrow stem cells, etc. Growing evidence suggests that adult pancreatic may include progenitor cells since it has the ability to self-recover after being subjected to harsh stimuli. The possibility of producing islet tissue in vitro for use in transplantation would be made possible by identifying and isolating these stem cells or progenitor cells[4].

The aim of this review is to further investigate the development of cells produced from stem cells for the treatment and cure of diabetes mellitus.

DISCUSSION:

Development of pancreas:

The pancreas is an organ in the abdomen. It is essential for converting the food we eat into energy for the body's cells. The exocrine (which aids in digesting) and endocrine (which controls blood sugar) functions of the pancreas are their two primary roles. It is derived from endoderm. In order for the endoderm to develop into the pancreas, it must interact with the surrounding mesoderm. For interaction with endoderm, mesoderm produces a variety of signaling molecules including FGH, BMP, Wnt, retinoic acid, nodal GATA4/6, FOXA2 and mix, hedgehog, notch, and set of SOX family. The development of the pancreas and the gut requires this connection. Numerous investigations are carried out to comprehend the many signaling routes and transcriptional factors involved in beta cell development, epithelial differentiation, and pancreatic organogenesis[11].

The foregut, midgut, and the hindgut are formed from endoderm. At the rear of the abdominal wall, a portion of the foregut and midgut creates a C-shaped loop. At the convergence of the foregut and midgut, two buds, designated as ventral and dorsal buds, arise. A 90-degree rotation of the c loop during development caused a shift in the positions of the bud. Later, the ventral budding rotates 180 degrees, fuses with the dorsal budding, and eventually forms a

whole pancreas[12]. The pancreatic epithelium then starts to compartmentalize, separating into tip and trunk domains. Multipotent pancreatic cells that later transformed into acinar-fated progenitors are seen in tip domains. Endocrine-duct bipotential progenitor pool is contained in trunk domains. The first transition phase is now complete[13]. Massive differentiation and lineage allocation take place in the second transition phase. Tip splitting is a process by which multipotential pancreatic cells at the tip differentiate into acinar cells. At the trunk, bipotential progenitor cells differentiate into endocrine cells. Differentiated endocrine cells combine to form clustered endocrine islets. Endocrine cells round up into mature islets in the last gestation and early post-natal life[14]. According to research by Bouwens and Rooman, alpha, delta, and PP cells surround the beta cells, which form the islet's core. Additionally, it is proposed that 80% of islet cells present at birth are created by the proliferation and differentiation of endocrine progenitors and 20% from islet cell proliferation. Islet cell maintenance follows a self-duplication mechanism after birth[15].

Neogenesis and replication are the two methods by which pancreas beta cells are formed. While neogenesis happens from active stem cells, replication happens from pre-existing beta cells. Beta cells are formed via replication rather than neogenesis, according to Dor and others[11].

Branched tubes that carry the enzyme generated by pancreatic acinar cells into the duodenum are lined by epithelial ductal cells of the pancreas. The capacity to produce endocrine cells may still be present in adult ductal cells, which resemble embryonic primitive ducts in certain ways[16]. Ductal cells express a transcriptional factor that helps in differentiation into beta cells. Additional research suggests that animals with diabetes mellitus can be treated with an islet cluster made from ductal cells[17]. Even the acinar cells in the pancreas can serve as progenitor cells and develop into beta cells[18].

Signaling Pathways for Growth, Development, and Differentiation of Beta Cells:

Signaling pathways that regulate endocrine pancreas development, proliferation, and differentiation are Hedgehog, Fgf, notch, Wnt, and TGF-beta[19]. The Hedgehog pathway plays a more important role and the Fgf signaling pathway helps in pancreatic growth and development during the emergence of mature islets[20,21].

Transcriptional factors for beta cell differentiation:

Beta cells are produced during the differentiation of pancreatic progenitor cells into endocrine precursors. This process involves a number of transcription factors. Pdx1 and pancreatic transcription factor 1a (ptf1a) are the two most significant transcriptional regulators[22]. The most significant marker, Pdx1, is essential for the endocrine and exocrine development of the pancreas. Recent research has demonstrated the significance of SOX4 in the generation of insulin from beta cells[23]. Additionally, SOX4 has been identified to control neurogenesis and maintain the pancreatic progenitor pool[24,25]. Endocrine pancreas development, proliferation, and survival depend on the transcriptional regulator islet-1[26]. Pax3, Ngn3, and HNF1 play key roles in maintaining islet progenitors[27]. The transcriptional factors Nkx2.2, Nkx6.1, Mafs, forkheads, and HNF4 are in charge of lineage specification and beta cell differentiation[28].

Introduction to stem cells:

Stem cells have the ability to develop into a range of cell types. Self-renewal and the capacity to differentiate into specialized adult cell types are two crucial traits of stem cells. Stem cells come in two types: pluripotent and multipotent. Pluripotent stem cells are those that can develop into any adult-type cell, while multipotent stem cells are limited to developing into certain cells. Pluripotent stem cells are only present for a very small amount of time during the development of an embryo. After that, they are converted into multipotent cells, which are more specialized, and finally into specialized tissues[29].

Because early research utilizing pluripotent stem cells on animals led to unique solid tumors known as teratomas, pluripotent stem cells are not yet employed in humans. Pluripotent stem cells from donors need to be immunosuppressed. Humans have been using multipotent stem cells extracted from bone marrow since 1960. Immunosuppressants are not necessary since multipotent stem cells are derived from the recipient body itself[31].

During embryo development, cells in the fertilized egg go through proliferation and specialization to form a blastocyst and then a gastrula that contains mesoderm, endoderm, and ectoderm. Stem cells are called embryonic stem cells and are pluripotent when obtained from the inner cell mass of the blastocyst. Pluripotent stem cells transform into multipotent stem cells as the blastocyst becomes a gastrula. Then grow into particular germ layers later - mesoderm, endoderm, and ectoderm[30].

Source of stem cells:

Pluripotent stem cells:

The embryo is used to obtain the pluripotent stem cells used today in research.15–20% of pluripotent stem cells are present in the inner cell mass of preimplantation embryos. These are collected and cultured in order to obtain more stem cells without losing their pluripotency. The most recent studies revealed that adult stem cells can reverse into a pluripotent stem cell known as an induced pluripotent stem cell [32].

Multipotent stem cells:

During gastrulation, when the human embryo is 14–15 days old, multipotent stem cells are present. Additionally, studies suggest that the cells can be found in the blood of the umbilical cord and placenta[31].

Outcomes of stem cells:

1. Quiescence: stem cell does not divide but maintain the stem cell pool

2. Symmetric self-renewal: stem cells divide into 2 daughter stem cells, both similar to parent stem cells resulting in an increase in the stem cell pool

3. Symmetric division without self-renewal: stem cell divides into two daughter cells, both are differentiated cells resulting in loss of stem cell pool

4. Asymmetrical self-renewal: stem cells divide into 2 daughter cells – one differentiated daughter cell and one stem cell, which maintain the stem cell pool[33].

A basic description of the several stem cell types:

Embryonic stem cells

Embryonal stem cells (ESC) are pluripotent cells with the capacity to develop into derivatives of all three germ layers (endoderm, mesoderm, and ectoderm). Teratoma development is the most typical test for proving pluripotency. Pluripotent stem cell lines, however, need to be able to meet a number of additional requirements. Stem cell lines may proliferate forever, display ESC markers, and have ESC-like shape[34]. ESCs are produced from totipotent cells found in the blastocyst, an early-stage mammalian embryo. These cells can proliferate in vitro indefinitely and without differentiation. ESC cell lines were predicted to be beneficial in drug development by Thomson et al in 1998[35].

Induced pluripotent stem cells

Induced pluripotent stem cells (iPSCs) are pluripotent stem cells that are created by reprogramming a non-pluripotent adult differentiated somatic cell. Initially, a pluripotent stem cell (iPSC) was created by triggering the "forced" expression of a few certain genes in an adult somatic cell[36]. Nuclear programming is also used for the generation of iPSCs, nuclear programming is a genetic engineering process where the right dose of transcription factors at the right duration is expressed in the right manner[37].

Morphologically similar to somatic cells, induced pluripotent stem cells can differentiate into a variety of other cells. Induced pluripotent stem cells are generated mainly from human fibroblasts[37]. ESC and iPSC are quite similar while having different origins. They have a lot of comparable growth traits, gene expression patterns, epigenetic changes, and developmental potential[38].

Somatic stem cells:

Multipotent somatic or adult stem cells (SSC) are seen in differentiated tissues. By replacing lost cells, these cells naturally maintain and regenerate aging or damaged tissue. SSC can be categorized into many categories according to their shape, cell surface markers, differentiation capacity, and/or tissue of origin[36]. Examples include endothelial progenitor cells (EPS), mesenchymal stem/stromal cells (MSC), and hematopoietic stem cells (HSC). The focus of somatic or adult stem cells has been on their capacity to divide or self-renew endlessly and to differentiate to produce all the specialized cell types of the tissue from which they came (with certain restrictions). For instance, neural stem cells are self-renewing multipotent cells that primarily produce nervous system phenotypes (such as neurons, astrocytes, and oligodendrocytes)[39].

Fetal stem cells:

The term "fetal stem cells" (FSC) refers to cells that can come from either a developing fetus or additional embryonic tissues. Teratomas are not created by fetal stem cells. Based on the tissues from which they originate (such as amniotic fluid, umbilical cord, Wharton's jelly, amniotic membrane, and placenta), several subtypes of fetal stem cells have been identified. Fetal stem cells are excellent sources for regenerative therapy because of their high multiplication rate and relatively simple accessibility. Given these characteristics, fetal stem

cells can be viewed as a functional and developmental intermediary between ESCs and SSCs[40].

Mesenchymal stem cells:

Mesenchymal stromal cells are a diverse population of non-hematopoietic progenitor cells that may develop into a variety of tissues. These are applied as promise-making tools for regeneration and repair[41]. MSCs, which were frequently obtained from bone marrow, were employed in the majority of clinical trials looking at stem cell treatment. This intense interest in MSC applicability for clinical approaches is based on their simple isolation from a variety of human tissues, including bone marrow, adipose tissue, placenta, and amniotic fluid, as well as their extensive capacity for in vitro expansion (up to 50 population doublings in just 10 weeks), as well as their multipotential differentiation capacity (osteoblasts, chondrocytes, and adipocytes)[42].

Stem Cell Therapy for Diabetes Mellitus

For the purpose of replacing damaged cells, several research studies have concentrated on creating insulin-producing cells (IPCs) from stem cells. The basic tactic relies on imitating the transcription factors that control the in vivo pathways that underlie pancreatic development. The pancreatic and duodenal homeobox 1 (PDX-1) transcription factor is a master regulatory transcription factor in pancreatic development, cell differentiation, and function. Pancreatic agenesis brought on by homozygous PDX-1 gene mutations results in persistent neonatal diabetes. Early-onset type 2 diabetes and maturity-onset diabetes of the young, or MODY 4, are both caused by heterozygous mutations of the PDX-1 gene.

PDX-1 controls the expression of the genes designated for endocrine progenitors during pancreatic development. In addition, PDX-1 activates the genes for insulin and is necessary for the survival, function, and proliferation of cells. Furthermore, by modifying transcription factors like PDX-1, some research has created functional IPCs. Together, these findings show how crucial PDX-1 is for cell function and differentiation.

Embryonic stem cells (ESCs) were the focus of substantial early stem cell research. However, doctors are hesitant to employ them in clinical settings due to the moral dilemmas surrounding the destruction of human embryos. Since 2007, when induced pluripotent stem cells (iPSCs) were successfully created from human fibroblasts, research has employed iPSCs to treat various conditions. Human iPSCs share the same pluripotent properties as ESCs but

are less controversial because they are produced from pre-existing somatic cells. One of the biggest challenges in the therapeutic application of iPSCs is immunological rejection following transplantation, which can be avoided by human iPSCs produced from autologous somatic cells. For therapeutic applications, it is crucial to create iPSCs directly from patients and increase their capacity to differentiate into functional target cells. Few studies, meanwhile, have shown the creation of IPCs from patient-derived iPSCs. Additionally, the majority of these investigations used iPSCs from healthy people or Type 1 Diabetes Mellitus patients[48].

Human embryonic stem cells and induced pluripotent stem cells are the most efficient sources of beta cells for the treatment of diabetes mellitus.

Beta cells derived from embryonic stem cells:

Human embryonic stem cells and induced pluripotent stem cells (iPSCs) are the most effective sources of beta cells for the treatment of Diabetes Mellitus[46].

Embryonic stem cells can be differentiated into insulin-producing beta cells by changing culture conditions. Embryoid bodies were cultured in vitro from collected mouse embryonic stem cells. Nestin-expressing embryonic stem cells were identified and stimulated to differentiate into beta cell phenotype. Phosphoinositide kinase inhibitors were added, speeding up this step. Along with this, transcription factors such as pdx1 or pax4 are introduced to produce outcomes. These differentiated cells have the ability to actively synthesize insulin. Studies on rodents have shown that injecting genetically modified embryonic stem cells into diabetic rats improves glucose regulation[43].

Pluripotent embryonic stem cells may be used as a start-up material for the in vitro production of beta cells. Because beta cells are derived from endoderm, embryonic stem cells first differentiate into endocrine cells before becoming beta cells.

Embryonic stem cells from a mouse were cultured under suitable conditions, and the presence of certain transcription factors associated with endodermal cell differentiation, such as HNF 4α and HNF 3β, were easily detectable. A trans factor that is endoderm and liver-specific, coup tf1, and a trans factor that is endoderm and pancreatic, pdx1, were also detected[44].

The first step in human embryonic stem cell differentiation is the formation of the Definitive Endoderm (DE) lineage, which is required for the production of the epithelium of the pancreas and other organs derived from the endoderm- liver, intestine, and lungs. According

to the study, the self-renewal cycle of hESC inhibition is the first step to be followed. Insulin, insulin-like growth factor (IGF), and FGF2 are essential for hESC to regenerate themselves, and the washing step inhibits them. Rapid differentiating of hESC to de is accomplished by nodal signaling. In the following step, transforming growth factor beta (TGF-β) is eliminated to effectively differentiate DE to foregut endoderm, which is supported further by FGF signaling. Utilizing FGF10 and FGF7, DE to foregut endoderm is effectively differentiated by expression of FOXA2, hepatocyte nuclear factor HNF4α, AND HNF 1α. The difference in foregut endoderm to pancreatic epithelium is related to a range of factors including PDX1, NKX6.1, PTF1, PROX1, HNF6, HLXB9, AND SOX9. NGN3 mRNA, which appears along with NKX2.2, undergoes an upregulation during the differentiation of foregut endoderm into the pancreatic epithelium. Hormone-expressing or producing cells rise quickly as a result. However, very few cells will express this. NGN3 is rapidly turned off by the NGN3/NKX2.2 positive cells as they develop into endocrine hormone-expressing cells and do not divide in culture[45].

Beta cells derived from induced pluripotent stem cells:

Induced pluripotent stem cells (iPSCs) can be used as a source of beta cells in diabetes mellitus. In cell culture, transcription factors aid in the differentiation of iPSCs into beta cells[37].

Pancreatic tissue for a study is sourced from legally authorized organ donation. Endoderm (the precursor of the pancreas) is created by isolating cells, reprogramming them using non-integrating vectors, and exposing them to a 4-day differentiation process. A 12-day differentiation technique is used on the best iPSC line after it has been chosen. An effective potential cell line for creating insulin-producing cells that are helpful for treating diabetes is the chosen iPSC line, SR1423[46].

A study generated induced pluripotent stem cells (iPSCs) using human skin fibroblast. Transcriptional factors like OCT3/4, SOX2, C-MYC, AND KLF-4 use retroviral carriers to reprogram human skin fibroblast into iPSCs. SeV (Sendai Virus), episomal vectors, and synthetic mRNA were the most frequently employed vectors for introducing transcriptional genes into the human skin fibroblast. Synthetic mRNA reprogramming is said to be the safest approach because it doesn't require plasmid or viral DNA. Insertional mutagenesis is reportedly a drawback of retroviral carriers.

Although skin fibroblasts can also be employed, blood cells are usually favored because of their ease of accessibility. A significant number of iPSCs can be generated from blood cells that are able to develop into beta cells. To regulate glucose levels, a receiver needs between 5,000 and 10,000 Islet Equivalents (IEQ) per kg of body weight.

Five phases are involved in the differentiation of iPSCs into beta cells:

1. Development of Definitive Endoderm

2. Development of the primitive gut tube

3. Development of pancreatic progenitors

4. Development of endocrine progenitors

5. Development of insulin-producing beta cells

- In the presence of activin A and low serum levels, induced pluripotent stem cells differentiate into definitive endoderm.
- Expression of PDX1, NKX 6.1, NEUROD1, and NKX2.2 leads to differentiation into pancreatic progenitors.
- Growth factors and small chemicals such as ALK5 inhibitors, BMP receptor inhibitors, and thyroid hormones have an impact on these transcriptional factors.
- To control the direction of insulin production, a notch inhibitor is administered[47].

In a study concluded by Min Jung Kim et al. punch biopsies (3 mm) were used to collect human fibroblasts from the buttocks of participants. By transducing a lentiviral system harboring the human SOX2, hOCT3/4, hKLF4, and hC-MYC genes into fibroblasts, human iPSCs were produced. Colonies were identified as distinct cell lines and were given the passage 1 designation. The cultured iPSCs were passed through more than ten times. In the beginning, cells were kept in a xeno-free environment and allowed to multiply in an undifferentiated form. Every time, the medium changed. It has been shown that sequentially turning on and off Ngn3, PDX-1, and MafA along the pancreatic development pathway causes generated human iPSC cells to become cells that secrete insulin like those found in the pancreas[48].

In this investigation, they showed that either Type 1 DM or Type 2 DM-specific iPSCs had the ability to produce functional IPCs, which did not significantly vary from the IPCs of ND-specific iPSCs. This raises the prospect of autologous transplantation using iPSCs in Type 1

DM and Type 2 DM patients. Here, Ad-PDX-1/VP16 was transfected to hasten the differentiation of human iPSCs into IPCs. As a result, human iPSCs could differentiate into IPCs that could respond to hyperglycemia in just two weeks [49]. Similar to ND-specific iPSCs, functional IPCs may be produced from Type 1 diabetes and Type 2 Diabetes -specific iPSCs. Our results are important because they show that people with both type 1 and type 2 diabetes may be candidates for autologous transplantation. For iPSCs to be used in therapeutic settings, collecting cells in a non-invasive and more practical approach is important in addition to boosting efficiency and maturity[50].

Beta cells derived from hemopoietic cells:

Certain cells in bone marrow migrate into the liver, gut, lung, skin, skeletal muscle, heart muscle, and central nervous system where they mature into parenchymal cells. Pancreatic islets produced from the donor's bone marrow were discovered in mice that had received bone marrow transplants and were evaluated 1-2 months later. In the presence of glucose, these cells secreted insulin and had intracellular calcium variations akin to those of typical beta cells[51].

Studies on diabetic animals have revealed that bone marrow stem cells occasionally develop into beta cells and endothelial cells. It was anticipated that the proliferation of nearby pancreatic progenitors would be stimulated by these endothelial cells, increasing insulin output. However, the loss of beta cells in people with autoimmune type 1 diabetes mellitus affects this approach. When bone marrow transplantation is carried out in non-obese diabetic rats prior to the onset of autoimmune diabetes, it produces micro chimerism. Chimerism stops host cells from turning into beta cells auto-reactive. Induction does not cause diabetes in animals who are not diabetic to go away[52].

In research done on Wistar rats, Osama M. Ahmed et al. evaluated the effectiveness of mesenchymal stem cells generated from bone marrow in the treatment of streptozotocin-induced type 1 diabetes mellitus. Mesenchymal stem cells generated from bone marrow have demonstrated a notable improvement in glycemic status, insulin, C-peptide levels, fructosamine, liver glycogen content, glucose 6-phosphatase activities, hepatic oxidative stress, and mRNA expression of NF-KB, IL-1β, IL-10, P53, and BCI-2 in pancreatic tissue. Their capacity to improve pancreatic islet architecture may serve as a mediator for the antihyperglycemic action[53].

Beta cells derived from mesenchymal cells:

Mice with streptozotocin-induced type 1 diabetes were utilized by Veronika S. Urban and coworkers. Blood sugar and serum insulin levels were brought back to normal following the administration of bone marrow and mesenchymal stem cells. Mesenchymal stem cells and bone marrow cells were ineffective on their own. Pancreatic insulin-secreting cells generated from recipients were stimulated to regenerate by bone marrow cells and mesenchymal stem cells. The immune response from T cells against freshly generated cells is suppressed by mesenchymal cells[54].

Mesenchymal stem cell (MSC) transplantation has been proven in several animal trials to be an effective treatment for type 1 diabetes-related hyperglycemia. Nearly all organs and tissues include mesenchymal stem cells, multipotent cells that may develop into a range of cell types. Due to these characteristics and the simplicity with which these cells may be extracted from bone marrow, MSCs are frequently employed in tissue repair for a number of disorders. The effects of MSC therapy were examined in 2014 research on diabetic rats. Five groups of male Wistar rats were created: the normal control, the diabetic control, the MSC and supernatant treatment group, and the MSC and supernatant treatment group. The MSCs that were implanted in some of the rats for this experiment provided the supernatant. In comparison to the diabetic control group over a period of weeks, the MSC-treated diabetic rats exhibited lower blood glucose levels and greater insulin levels. Rats given supernatant treatment also exhibited lower blood sugar levels, but not as much. The rats treated with MSC and supernatant showed the highest reduction in their blood sugar and insulin levels. MSC-treated, supernatant-treated, and MSC and supernatant-treated rats all had partly regenerated pancreatic tissues, and new and bigger islets of Langerhans were observed, according to an immunohistochemical study of the pancreatic tissues from the rats. The study's findings and the immunohistochemistry analysis indicated that the MSCs underwent differentiation into beta cells that produce insulin. As a result, the MSC-treated rats experienced lower blood sugar and higher insulin levels. The study also demonstrated that growth factors, cytokines, and chemokines released by MSCs and found in the supernatant might aid in pancreatic cell repair and regeneration; however, this study had a number of drawbacks that prevented it from being used in the treatment of diabetes in people.

First of all, the study only used male rats; there may be sex differences that affect females differently for known or unknown reasons. Second, the study discovered that several MSC

injections were more beneficial than a single injection. It may be difficult and expensive to establish a treatment that requires several, continuing injections if stem cell therapy for diabetes were used on people. It is also important to note that during this trial, the diabetic control group rats lost weight on average, but the MSC-treated rats gained weight on average. This could be because when the stem cells developed into insulin-producing cells, the rats treated with MSCs showed improved glucose absorption. When this weight increase occurs in people, it could not be good for the management of type 2 diabetes. Obesity and type 2 diabetes are closely related; therefore, weight increase would not be a good result of stem cell treatment. However, the weight increase seen in this study might be advantageous for people with type 1 diabetes who have recently been diagnosed and have lost weight as a result of their cells' inability to take up glucose[55].

Beta cells derived from adipose stem cells:

A study compared the phenotype and functionality of Adipose Stem Cells (ASCs) isolated from mice with leptin receptor-deficient (db/db), high-fat diet-induced type 2 diabetes, and streptozotocin (STZ)-induced T2D with cells from healthy C57BL/6 mice in order to evaluate the potential therapeutic effects of adipose tissue-derived mesenchymal stem cells (ASCs) for the treatment of type 2 diabetes (T2D). Similar cellular marker expression patterns and the capacity to develop into adipocytes, osteoblasts, and chondrocytes were seen in ASCs from T2D or db/db animals. The rate of proliferation, nevertheless, was slower. Hepatocyte growth factor (HGF) secretion was decreased in ASCs from db/db mice. Through 5 weeks post-infusion, T2D mice who received a single intravenous injection of T2D or db/db ASCs showed improved insulin sensitivity, decreased hepatic inflammation and fat content, and increased pancreatic cell mass[56].

2D culture and 3D culture for beta cell differentiation:

In one experiment, beta-fibroblast growth factors, epidermal growth factors, beta cellulin, and activin A were used as transcription factors and signal molecules to treat human mesenchymal cells. The presence of proinsulin C peptide in the cells in the solution suggested that mesenchymal stem cells had differentiated into beta cells. The number of mesenchymal stem cells developing into beta cells increases as the number of growth factors supplied to the cells rises. It has been discovered that 3D Cultures are more successful since they are created in a manner that replicates natural beta cells. Fibrin glue, a fibrous protein comprised of fibrinogen and thrombin, is used to create 3D cultures. The scaffold matrix made by the fibrin

glue allowed mesenchymal stem cells to differentiate and grow. Transcriptional factors were applied to both 2D and 3D cultures employed in the study. IPCs (insulin-producing cells) from the 2D culture were flat and elongated, but IPCs from the 3D culture were rounded and closely resembled beta cells. IPCs from the 3D culture were better able to normalize blood glucose after being injected into male Wistar rats from both 2D and 3D cultures[57].

Stem cell therapy for diabetes mellitus complications:

The most frequent consequence of diabetes mellitus is thought to be diabetic polyneuropathy (DPN). Diabetes mellitus can result in diabetic feet, which can lead to ulcers, infections, and limb amputations. There are three different types of DPN: painful DPN, atypical diabetic polyneuropathy, and normal diabetic polyneuropathy. It has been shown that DPN benefits from stem cell treatment. Induced pluripotent stem cells, embryonic stem cells, bone marrow-derived cells, and dental pulp stem cells are all used in stem cell treatment. Using stem cells, the blood vessels and peripheral nerves that have been injured can be repaired. To lessen discomfort and enhance blood supply to the nerves, growth factors and adult stem cells are injected into the injured regions [58].

Neurotrophic factors are released by transplanted stem cells to cure DPN. Due to ethical considerations and the possibility of tumor development, the use of hESCs is restricted. Bone marrow stem cells, induced pluripotent stem cells, and mesenchymal stem cells were used for the study. The production of neurotrophic factors from transplanted stem cells, such as epidermal growth factor, transforming growth factor-, VEGF, bFGF, hepatocyte growth factor, IGF-1, and BDNF, is one way that adipose tissue-derived stem cells might stimulate tissue healing. Patients with diabetic neuropathy were shown to have decreased expression of VEGF, bFGF, IGF-1, and BDNF[59].

Encapsulation technique for stem cell therapy:

The encapsulation approach is based on a matrix that permits the transport of nutrients, oxygen, and signaling molecules but inhibits immune cells, cytokines, and antibodies from responding to grafts. To avoid an immunological response against transplanted hPSC-derived pancreatic offspring, including allogenic grafts, an adequate encapsulation method is especially important for T1DM patients. The biocompatibility, stability, and selectivity of the membrane, interactions with the circulation, and availability of nutrients and oxygen, among other factors, should all be taken into account while evaluating an encapsulating device. The

major application of these studies, which were created for pancreatic islet transplantation, was to find the best materials to improve these qualities[60].

The major application of these studies, which were created for pancreatic islet transplantation, was to find the best materials to improve these qualities. Due to its biocompatibility, the scaffolding polysaccharide alginate generated by brown seaweeds is frequently used. Alginates are linear, unbranched polymers with D mannuronic Acid (M) and L-guluronic Acid (G) residues that exhibit exceptional gel-forming properties when in the presence of polyvalent cations like Ca^{2+} and Ba^{2+}. Purified alginate is used to encapsulate islets, which has been shown in earlier research to greatly increase survival, long-term biocompatibility, and function. Furthermore, certain alterations to alginates are of significant interest since they may be able to reduce the adverse effects of an allo- or xenograft transplant on the local immune system. By establishing prolonged local immunological isolation, the chemokine CXCL2 was combined with alginate microcapsules to protect allo- or xeno islet transplantation from immune responses. Recent research by the same team has proven that these modifications to alginates can effectively extend the survival and function of hPSC-derived cells and provide long-term immunoprotection in mice with T1DM who are immunocompetent and do not require systemic immunosuppression. Notably, CXCL2 improved β cells' GSIS activity, making it an important biomaterial to research[61].

Immunomodulation in stem cell therapy:

For the therapy of T1DM, human ESC/iPSCs-derived cells have been suggested as a viable source of replacement cells. However, autoimmune and alloimmune reactions continue to be a significant obstacle to the widespread use of cell replacement therapy for T1DM. Despite significant advancements in encapsulation technology, there are still difficulties in getting transplanted hPSC-derived pancreatic progenitors, or cells, to graft. If the encapsulating mechanism is removed, the immune system of the receiver will undoubtedly kill the engraftments. It seems hopeful to modify these encapsulated cells in certain ways to thwart autoimmune reactions. The primary molecular mechanism causing immune rejection in allo- or xenografts is HLA mismatching[62].

Studies have shown that removing HLA-A genes from hematopoietic stem cells using zinc-finger nucleases might improve donor compatibility. Similarly, deleting HLA-A and HLA-B biallelically or knocking out the β2-microglobulin (B2M) gene, which eliminates all HLA class I molecules, left one allele of HLA-C to enable the hPSC grafts to resist T and NK cell

assaults. There have been other methods for immunosuppressive effects that have been documented, such as the targeted overexpression of PDL1-CTLA4Ig in β cells, which successfully delayed the onset of T1DM and allo-islet rejection, hence enhancing the survival of the cell mass. Therefore, using hPSCs to modulate the immune system may be a viable way to address the problems caused by engraft rejection[63].

Clinical trials in stem cell therapy for type 1 diabetes mellitus:

Dr. Julio C. Voltarelli and his team of researchers published the results of the first clinical trial evaluating stem cell transplantation as a workable, secure, and efficient therapy for type 1 diabetes in 2007. In order to stop further loss of insulin-producing cells and enhance cell function in human patients, immunosuppression therapy pharmacologically suppressing the immune system to prevent an immune reaction against the transplanted cells—was prescribed after autologous nonmyeloablative hematopoietic stem cell transplantation (AHST). 15 individuals who had been diagnosed with type 1 diabetes within the preceding six months made up the sample population. Because individuals with a higher risk of complications may have safety concerns, patients with a history of diabetic ketoacidosis were excluded from the study. The 15 patients were monitored for seven to thirty-six months, which resulted in inconsistent follow-up. 14 individuals stopped taking insulin throughout the follow-up for varying amounts of time. Mean total C-peptide levels were considerably higher than patient baseline levels at six months post-treatment. Additionally, for 13 of the patients, hemoglobin A1c levels were kept below 7%. These findings support the use of AHST as a type 1 diabetes therapy[64].

Two years later, the same research team conducted a follow-up study to address some of the shortcomings of their initial investigation. The research featured a longer four-year follow-up period and included the initial 15 patients as well as an additional 8 participants in the sample. Patients who had experienced past ketoacidosis were not included in the treatment procedure, which was the same as in the 2007 trial. Twenty patients achieved insulin independence throughout the follow-up period (7 to 58 months), and 12 of those patients kept it for 14 to 52 months (mean 32 months). All patients had considerably higher C-peptide levels, and hemoglobin A1c levels were kept around 7%. These parameters are indicative of increased insulin production and β cell function, and the prolonged follow-up period showed sustained positive results of treatment[65].

In 2012, nine type 1 diabetes individuals who had just received their diagnosis participated in a research experiment. Given prior problems, the study concentrated on the possible advantages of stem cell therapy in order to optimize treatment and choose a patient population that would benefit most. Two groups were found 12 months after AHST: 6 patients who were no longer insulin-dependent and 3 patients who were still insulin-dependent but on a lower dosage. Patients who were insulin-independent produced considerably more C-peptide and showed more genomic events than were AHST-modified. Each group's top pathways and co-expression networks exhibited unique related patterns. These different transcriptional processes in peripheral blood mononuclear cells may be the cause of the variation in patient responses to therapy. Further immune cell population research by the study indicates that the reduction of islet-specific autoreactive T cells may be the cause of improved islet function in newly diagnosed type 1 diabetics after therapy [66].

42 individuals, aged 18 to 40, with a history of T1DM for less than two and sixteen years, were randomly assigned to the routine insulin care therapy group and the stem cell transplantation group between January 2009 and December 2010. According to a 1-year follow-up test, insulin climbed in treated patients while it fell in control patients. The C-peptide also increased in treated patients while it declined in control groups. Furthermore, HbA1c and fasting glycemia rose in the control participants whereas they fell in the treatment groups. In comparison to the control groups, the treated groups' daily insulin needs also dropped. Patients reported a considerable reduction in the number of severe hypoglycemia incidents over the follow-up period[67].

Clinical trials in stem cell therapy for type 2 diabetes mellitus:

In 2008, 25 patients with type 2 diabetes participated in clinical trial research that combined intrapancreatic autologous stem cell (ASC) infusion therapy with hyperbaric oxygen therapy (HBO). During the follow-up period, there was an increase in C-peptide and a drop in hemoglobin A1c readings. Additionally, post-treatment needs for both injectable insulin and oral hypoglycemic medication were reduced. The fact that BMI stayed mostly constant over the course of the trial implies that benefits were not only due to physician monitoring, food, exercise, and diabetes treatment. According to this study, people with type 2 diabetes may see notable advantages while receiving ASC together with HBO therapy [68].

The most current clinical studies were carried out by Dr. Bhansali and other experts in 2014. The original study involved 21 patients with type 2 diabetes and was a randomized, single-

blinded, controlled clinical trial examining the outcomes of autologous bone marrow-derived stem cell transplantation (ABMSCT). On 10 patients, a follow-up study was done. The 21 patients were split into experimental and control groups at random in the initial research. At 3, 6, and 12 months after treatment, there was a substantial difference in the insulin dosage between the experimental and control groups, with the experimental group demonstrating a mean 66.7% reduction in insulin demand. It was demonstrated that a rise in C-peptide was positively and substantially correlated with a decline in insulin needs. The most current clinical studies were carried out by Dr. Bhansali and other experts in 2014. The original study involved 21 patients with type 2 diabetes and was a randomized, single-blinded, controlled clinical trial examining the outcomes of autologous bone marrow-derived stem cell transplantation (ABMSCT). On 10 patients, a follow-up study was done. The 21 patients were split into experimental and control groups at random in the initial research. At 3, 6, and 12 months after treatment, there was a substantial difference in the insulin dosage between the experimental and control groups, with the experimental group demonstrating a mean 66.7% reduction in insulin demand. It was demonstrated that a rise in C-peptide was positively and substantially correlated with a decline in insulin needs[69].

Challenges in stem cell therapy for diabetes mellitus:

Before they can be utilized as routine treatments, β cell-based medicines must still pass a number of obstacles as they are still in the experimental stage. It was difficult to overcome some of the hazards and adverse effects of β cell treatment that are brought on by islet transplantation into the hepatic portal vein. Certain unfavorable consequences are seen when ESC is transplanted into humans following differentiation.

- Risk of tumor development before being used in humans, stem cell treatments must be studied in animal models since they can result in tumors like teratomas. Transplanting completely developed, pure cells made from hESCs is the best solution[70].
- Immature cells have the following drawbacks: In vitro creation of IPCs from hECSs is immature, and glucose homeostasis is insufficient, which defeats the aim. In contrast to in vitro, cell-to-cell interactions are often absent under in vitro circumstances. The environment they live in is a key distinction between beta-cells found in the pancreas and those produced in vitro[71].
- When islet tissue is transplanted, there are two different challenges to overcome in terms of transplant rejection. The control of autoimmune is essential for the effectiveness of cell

replacement treatment because autoimmunity kills -cells in people with type 1 diabetes. Alloimmune host vs. graft reactions are brought on when the immune system perceives transplanted tissue as alien[72].

CONCLUSION:

Even though adult progenitor cells have very limited capacity for self-renewal and the generation of different cell types, their capacity to rebuild tissue during regular turnover or following harm is of great interest. The key is in the signaling pathways and transcription factors that convert progenitor cells into beta cells that produce insulin. Although islet transplantation has given patients with type 1 diabetes and, to a lesser extent, type 2 diabetes fresh hope for a cure, its potential for long-term treatment for diabetics is limited by ongoing transplant rejection issues. Therefore, new diabetes therapy options are now possible because of research, therapeutic consideration, and technology to identify, isolate, purify, and characterise adult cells. However, before Embryonic Stem Cells may be employed extensively in a therapeutic environment, several obstacles must be met and overcome. The following four issues are among the biggest ones:

A) How to differentiate hPSCs into Insulin Producing Cells more effectively, and how to shield implanted IPCs from autoimmune attacks

B) How to produce enough of the desired cell types for clinical transplantation, and how to generate sufficient numbers of desired cell types

C) How to establish complete insulin independence

Today, cell replacement treatment for people with type I and type II diabetes has emerged as a realistic possibility that could be realized soon. Although there has been progress, there are still significant gaps in our knowledge of adult beta-cell dynamics and the pancreas developmental biology that must be filled before a therapeutic application can be achieved.

ACKNOWLEDGEMENT

“Devoting the necessary time and effort is a crucial element on the path to achieving success”. I am profoundly thankful to the Almighty and my parents for providing me with the support needed to meticulously complete this comprehensive analysis. My heartfelt appreciation goes out to the numerous individuals who contributed their time and encouragement during this extensive review.

I am grateful to all those with whom I had the privilege of collaborating during this analytical review. My special thanks go to the computer operators and other professionals who provided technical assistance and ensured the timely preparation of this manuscript.

Last but not least, I want to express my extensive appreciation to everyone who has been directly or indirectly connected to my research.

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