STEM CELL THERAPY IN TYPE1 DIABETIC TREATMENT: CURRENT ADVANCEMENT AND FUTURE PROSPECTIVE

Abstract

Type 1 diabetes is a chronic autoimmune disease that destroys insulin-producing beta cells in the pancreas, leading to poor blood sugar regulation. Traditional treatments, like insulin therapy, often struggle to achieve long-term glucose control. Stem cell therapy offers a promising alternative, with the potential to restore beta cell function and provide a permanent solution for managing the disease.This paper ***aims*** *to explore the role of stem cell therapy, advancements and research findings, potential benefits and challenges associated with this therapy in Type 1 Diabetes treatment. The****methodology****of this review study have used a combination of experimental studies, clinical trials, and literature reviews to compile the findings. They present data from pre-clinical and clinical studies that demonstrate the capability of stem cells to restore insulin production in animal models, alongside early-phase clinical trials showing potential in human subjects.****The finding****of thisstudy shows; Stem cell therapy offers promise for treating type 1 diabetes through successful differentiation of various stem cell sources into functional beta cells. Clinical trials have demonstrated positive outcomes, including improved glycemic control and reduced insulin dependency. However, challenges of immune rejection and tumorigenicity require attention. Researchers are actively exploring immune modulation and encapsulation strategies to protect transplanted cells.* ***In conclusion****Stem cell therapy for Type 1 diabetes shows promise in creating functional beta cells to improve glucose control and reduce insulin reliance. While challenges like immune rejection and tumor risks remain, future efforts aim to enhance cell functionality and personalize treatments.*

Key words:*Insulin,Pancreatic beta cells, Stem celltherapy and T1 DM*

Graphical abstract

Recent advancements in Type 1 diabetes treatment focus on developing stem cell-derived beta cells to replace damaged insulin-producing cells. Improved transplant techniques aim to integrate these cells into the pancreas for stable insulin production. Future strategies include engineered cells that resist autoimmune responses, reducing the need for immunosuppressive drugs, and personalized therapies tailored to individual patient needs. Together, these innovations represent significant progress toward effective and potentially curative treatments for Type 1 diabetes.

1. INTRODUCTION

1.1. Background

Diabetes mellitus is a global public health issue both developing and developed countries, leading to increased morbidity and mortality rates worldwide (1). It is a chronic metabolic disorder characterized by elevated blood glucose levels due to either insufficient insulin production or impaired insulin function (2). Insulin is a hormone produced by the pancreas that regulates the amount of glucose in the bloodstream and facilitates its entry into cells to be used as energy(3).Insulin-producing cells are primarily located in clusters of cells called the islets of Langerhans within the pancreas. The islets of Langerhans contain different types of cells, including alpha cells (which produce glucagon), and beta cells (which produce insulin) (4).

According to the International Diabetes Federation(IDF), approximately 463 million people worldwide had diabetes in 2019, with the number expected to reach 578 million by 2030 and 700 million by 2045 as the stated in the paper of (5).As the stated in the paper of (6)In Ethiopia, the WHO estimated 800,000 diabetics in 2000, projecting an increase to 1.8 million by 2030.

Type 1 diabetes (T1D) is an autoimmune disease where the body's immune system mistakenly attacks and destroys the insulin-producing beta cells in the pancreas. This leads to an inability to produce insulin, a hormone essential for regulating blood sugar levels (7). Insulin, produced by the pancreas, regulates blood sugar levels by promoting glucose uptake and utilization in cells throughout the body, serving as an energy source or stored as glycogen (8).T1D can develop at any age, but it is most commonly diagnosed in children, adolescents, and young adults. The exact cause of T1D is not fully understood, but it is believed to involve a combination of genetic and environmental factors.T1D is more common in individuals with a family history of the disease and in those with certain genetic markers (9).

Uncontrolled type 1 diabetes mellitus (T1DM) can lead to serious complications such as diabetic ketoacidosis (DKA) a life-threatening condition characterized by high blood sugar and ketone buildup, can result in coma or death if untreated, severe hypoglycemia in cells,cardiovascular disease, diabetic retinopathy, diabetic nephropathy, and diabetic neuropathy (10).

The treatment for type 1 diabetes involves lifelong insulin therapy, as the body cannot produce insulin on its own. Insulin is typically administered through injections or an insulin

pump to help regulate blood sugar levels and prevent complications such as diabetic ketoacidosis, nerve damage, eye issues, kidney disease, cardiovascular disease, foot problems, high blood pressure, stroke, and heart attack. Howeveravailability of traditional treatments such as exogenous insulin injection. These methods can only alleviate the symptoms but cannot cure diabetes

completely (11, 12) and has side effects and imposing a heavy financial burden on individuals, their families, and society as a whole (12).There for, this review will focused on steam cell therapy in type1 DM treatment for minimize such like side effects.

2. OBJECTIVES

2.1. General Objectives

- To explore the role of stem cell therapy, advancements and research findings, potential benefits and challenges associated with this therapy in Type 1 Diabetes treatment.

2.2. Specific Objectives

- To explore the role of stem cell therapy in Type1 Diabetes treatment.
- To discuss the latest advancements and research findings related to the use of stem cells in managing Type1 Diabetes.
- To highlight the potential benefits and challenges associated with this therapy.

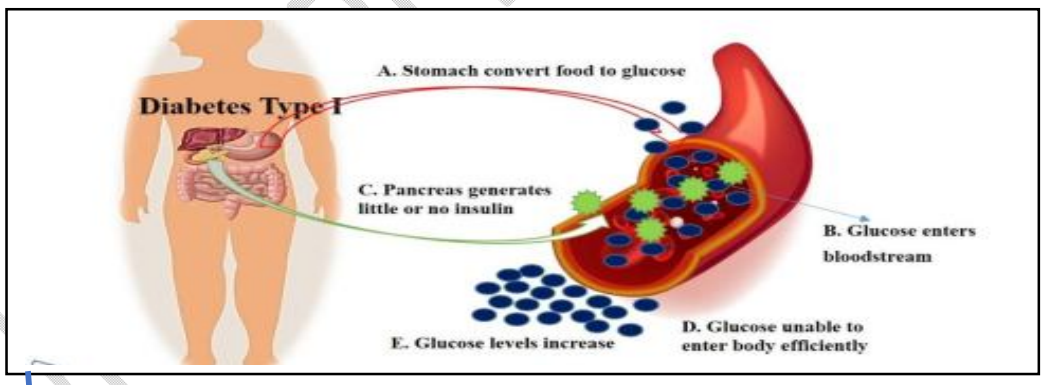
3. Type1 Diabetes Mellitus

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by elevated blood glucose levels, either due to insufficient insulin production or impaired insulin function (1). Insulin is a hormone produced by the pancreas that regulates the amount of glucose in the bloodstream and facilitates its entry into cells to be used as energy (3).

Here are mainly the three types of diabetes:each with distinct causes, onset times, insulin production levels, treatments, and risks. Type 1 diabetes is an autoimmune disease that destroys insulin-producing cells in the pancreas, usually diagnosed in childhood or adolescence. Treatment involves lifelong insulin injections for blood sugar regulation (13).Type 2 diabetes is primarily caused by lifestyle factors such as obesity and inactivity, along with genetic predisposition and it is more common in adults. The pancreas initially produces insulin, but the body later becomes resistant to it.Management involves lifestyle changes, medications, and insulin therapy (13). Gestational diabetes occurs during pregnancy due to hormonal changes, resulting in insulin resistance, and can be managed through diet, exercise, and potentially insulin therapy, with increased risks for both mother and baby and potential long-term implications (13).

Type 1 diabetes (T1D) is an autoimmune disease where the body's immune system mistakenly attacks and destroys the insulin-producing beta cells in the pancreas. This leads to an inability to produce insulin, a hormone essential for regulating blood sugar levels (7). Despite the availability of traditional treatments such as exogenous insulin these methods can only alleviate the symptoms but cannot cure diabetes completely (11, 12). The disease has a significant impact on patients' daily life, requiring constant monitoring of medication side effects and imposing a heavy financial burden on individuals, their families, and society as a whole and it has associated with several side effects, including: Hypoglycemia, weight gain, Insulin resistance and gastrointestinal side effects(12).

Consequently stem cell-based therapy has shown considerable promise as a future therapeutic modality for diabetes mellitus and its complications (11). However, there are still challenges and limitations to be addressed, such as the lack of standardized protocols for stem cell transplantation, the potential risks of immune rejection, and the need for further clinical trials to establish the safety and efficacy of different types of stem cells in treating diabetes (11).Therefore, the paper aims to explore the current advancements and future prospects of steam cell therapy in type 1 diabetic treatment, focusing on the types of stem cells that have the most successful evidence in treating diabetes and assessing the safety and efficacy of different types of stem cells in the treatment of diabetes mellitus (11, 12).



In T1DM stem cell therapy insulin producing beta cells

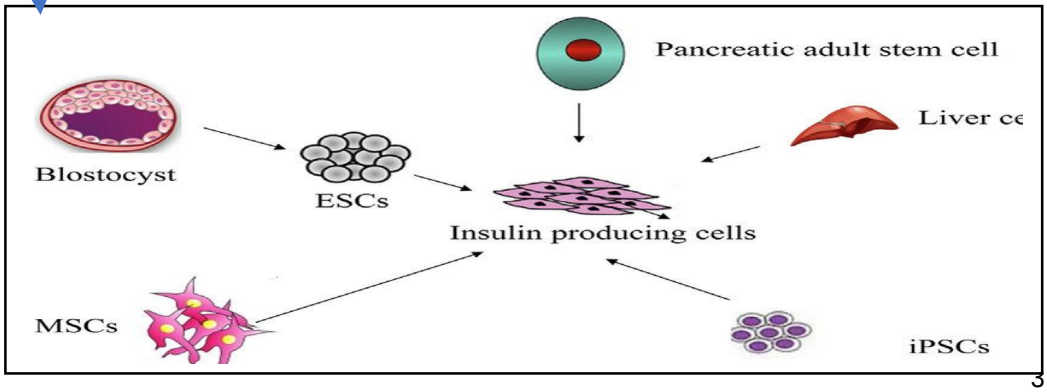


Figure 1. Stem cell therapy insulin producing beta cells(14, 15)

Type 1 diabetes mellitus (T1DM) is an autoimmune condition characterized by the destruction of insulin-producing beta cells in the pancreas. This leads to insulin deficiency and chronic hyperglycemia, as indicted in **figure 1** which can result in severe complications such as diabetic nephropathy, neuropathy, and retinopathy(16).Stem cell therapy is emerging as an effective way to prevent the destruction of insulin-producing beta cells in the pancreas, a hallmark of type 1 diabetes (T1DM). The goal of this treatment is to restore insulin production and improve blood sugar control in patients with this autoimmune disease (17); which is described in the **figure 1**.

The classical treatment for type 1 diabetes (T1DM) is insulin replacement therapy(18), which involves administering exogenous insulin to regulate blood glucose levels. This can be done through multiple daily injections (MDI) using syringes or pens, or through continuous subcutaneous insulin infusion (CSII) using an insulin pump. Rapid-acting insulin is given at mealtimes, while long-acting insulin provides a steady background level(19). Patients must closely monitor their blood glucose levels, typically using finger stick checks or continuous glucose monitoring (CGM), and adjust insulin doses accordingly(20). Lifestyle modifications like healthy eating and regular physical activity are also important components of T1DM management(21), and adjunctive medications like pramlintide, metformin, and GLP-1 agonists may provide additional benefits in some patients(20). Despite these efforts, many patients struggle to maintain optimal blood glucose control and avoid complications like hypoglycemia, driving research into novel treatments(20).

Pharmacological treatments for type 1 diabetes mellitus (T1DM) encompass a range of medications and therapies aimed at managing blood glucose levels and improving overall health outcomes. Insulin remains the cornerstone of treatment, with various types available, including rapid-acting, short-acting, intermediate-acting, long-acting, and ultra-long-acting insulin, each serving specific purposes in regulating glucose levels(22). Additionally, adjunctive therapies like pramlintide, metformin, GLP-1 receptor agonists, and Sodium-glucose co-transporter 2(SGLT2) inhibitors are being explored to complement insulin therapy and address metabolic conditions associated with T1DM(23). These adjunctive medications

offer benefits such as improved glycemic control, reduced insulin needs, weight loss, and potential cardiovascular risk reduction. The evolving landscape of pharmacological treatments for T1DM underscores the importance of individualized approaches to therapy, considering both efficacy and potential adverse effects when selecting treatment options(22).

The primary side effect of the classical treatment for type 1 diabetes (T1DM), which centers around intensive insulin therapy, is the increased risk of hypoglycemia (low blood sugar). As the disease progresses, patients often develop hypoglycemia unawareness and lose their normal counter regulatory defenses, leading to a 3-fold excess of severe hypoglycemic episodes compared to the general population(24). Maintaining tight glucose control with insulin therapy heightens this risk, as the search results emphasize that hypoglycemia is the "primary obstacle to achieving optimal glycemic control" in T1DM and it has also economical side effect. These dangerous low blood sugar events can be life-threatening if not properly managed, significantly hindering the ability to regulate blood glucose levels effectively in these patients (24, 25).

The treatment landscape for type 1 diabetes (T1DM) is evolving, with several promising new therapies in development beyond the standard insulin replacement therapy. Immunotherapies aim to stop or slow the autoimmune destruction of beta cells, with therapies that interfere with T cell activation appearing most promising, such as anti-thymocyte globulin (ATG) and granulocyte colony stimulating factor (GCSF)(26). Regenerative therapies seek to replace lost beta cells, with mesenchymal stem cell (MSC) therapy showing beneficial effects through immune regulation, though clinical trials are limited, and islet transplantation from deceased donors being an exciting but donor-limited prospect(27). Future directions likely involve combination therapies integrating immunotherapies, regenerative approaches, and medications like GLP-1 agonists and SGLT2 inhibitors, with identifying biomarkers to predict responders and tailoring interventions to disease stage and patient age being important(28). While many promising therapies have fallen short so far, the knowledge gained has paved the way for better

In vitro*:* In vitro refers to experiments or procedures performed in an artificial or controlled laboratory environment, usually involving cell cultures or isolated tissues. In stem cell therapy, the behavior, properties and differentiation potential of stem cells are studied using in vitro techniques(29). Scientists can grow stem cells in a laboratory dish, provide them with special growth factors or culture conditions, and observe their reactions. In vitro studies can provide valuable information about the properties of stem cells and their potential applications in therapy(30).

In vivo: In vivo refers to experiments or procedures that take place in a living organism. In stem cell therapy, in vivo means giving or transplanting stem cells directly into the patient's body(31). This may involve injecting stem cells into certain tissues or organs. Stem cells interact with the host's biological systems, potentially differentiating into specialized cell types and promoting tissue regeneration or repair(29).

3.1. Epidemiology of Type 1 Diabetes Mellitus

Type 1 diabetes mellitus (T1DM) is a significant global health concern characterized by autoimmune destruction of insulin-producing beta cells in the pancreas. This section outlines the epidemiology of T1DM, starting from global statistics and narrowing down to the situation in Ethiopia (32).

In 2021, approximately 8.4 million individuals worldwide were living with T1DM, with projections suggesting this number could rise to between 13.5 million and 17.4 million by 2040. The majority of cases occur in adults, with about 64% of individuals aged between 20-59 years (33).The global incidence of T1DM is increasing, with around 500,000 new cases diagnosed in 2021. The incidence varies significantly by region, with Northern Europe reporting the highest rates, particularly among children aged 0-14 years (34).Individuals diagnosed with T1DM face higher mortality rates compared to the general population. In low-income countries, the average life expectancy for a 10-year-old diagnosed with T1DM is only 13 years, while in high-income countries, it can extend up to 65 years (34)

In Ethiopia, the estimated prevalence of T1DM among children and adolescents aged 0–19 years is approximately 2.4 per 100,000 annually. This figure reflects a growing recognition of diabetes among younger populations in the country. The number of new cases of T1DM is on the rise in Ethiopia, similar to global trends. The International Diabetes Federation (IDF) reported that as of 2021, about 108,300 children under 15 years are diagnosed globally each year, contributing to the increasing burden seen in Ethiopia as well (32).

Despite the rising prevalence and incidence rates, healthcare infrastructure and access to diabetes management resources remain limited in Ethiopia. This results in significant challenges for effective disease management and contributes to premature mortality among individuals with T1DM(35). Studies indicate that children and adolescents with T1DM in Ethiopia experience various challenges related to disease management, including dietary restrictions and frequent monitoring of blood glucose levels. Factors such as parental education and socioeconomic status significantly influence their health-related quality of life (HRQoL). Understanding the epidemiology of T1DM from a global perspective down to

local contexts like Ethiopia is crucial for developing targeted health policies and interventions aimed at improving outcomes for affected populations(32).

3.2. Stem Cells Classification

Stem cells can be classified based on potency and sources. Based on potency, stem cells are classified as totipotent, pluripotent, multipotent, oligopotent, and unipotent(36).

3.2.1. Based on potency

Totipotent

Totipotent stem cells are a type of stem cell with the ability to differentiate into any cell type in the human body, including extra-embryonic cells crucial for fetal development(37).In essence, totipotent stem cells possess the potential to give rise to a complete and functional organism. During early embryonic development, the single-cell zygote is totipotent, able to give rise to all body cells, including those of the embryo, placenta, and supportive tissues. When the zygote divides into a blastocyst, the inner cell mass contains totipotent cells capable of generating all cell types(36, 38).

Pluripotent

The ability to turn almost all cell types. Examples include embryonic stem cells and cells derived from the germ layers of mesoderm, endoderm, and ectoderm that develop during the early stages of embryonic stem cell differentiation.The mesoderm, endoderm, and ectoderm are the primary germ layers formed during embryonic development. Each germ layer gives to different tissues and organs in the body(36).

Multipotent

Multipotent stem cells are a type of stem cells that are capable of differentiating into a limited number of cell types in a specific tissue or organ(37). Unlike pluripotent stem cells, which can differentiate into any cell type in the body, pluripotent stem cells can give rise to only a few closely related cell types. Examples of multipotent stem cells are hematopoietic stem cells (HSC) found in the bone marrow, mesenchymal stem cells (MSC) found in various tissues, and neural stem cells found in certain brain regions. These cells have therapeutic potential in regenerative medicine, cell transplantation, and tissue engineering (39).

Oligo potent

Oligopotent stem cells are able to self-renew and form 2 or more lineages in a given tissue; For example, the surface of the pig eye, including the cornea, is said to contain oligopotent stem cells that generate single colonies from corneal and conjunctival cells(37). Hematopoietic stem cells are a typical example of oligopotent stem cells because they can differentiate into both myeloid and lymphoid lineages. Studies of the lung show that

bronchoalveolar duct junctional cells can give rise to bronchial epithelium and alveolar epithelium (40).

Unipotent

Unipotent stem cells can self-renew and differentiate only into one specific cell type and form a single lineage, for example muscle stem cells, resulting in mature muscle cells and not other cells(40).

3.2.2. Based on their sources

Embryonic stem cells

Embryonic stem cells are derived from embryos that are typically 3 to 5 days old. These cells are pluripotent, meaning they have the ability to differentiate into almost any cell type in the body(37).ESCs are characterized by their unlimited self-renewal potential, meaning they can divide and replicate indefinitely while maintaining their pluripotent state. Due to their remarkable differentiation ability, ESCs have been widely studied for their potential applications in regenerative medicine, disease modeling, and drug discovery (40).

Adult stem cells

Adult stem cells (ASCs) found in specific tissues in the body like bone marrow, adipose tissue, and umbilical cord(41). adult stem cells are found in small numbers in various tissues of adult organisms. Adult stem cells are multipotent, which means they are more restricted in their differentiation potential compared to embryonic stem cells. Adult stem cells can differentiate into specific cell types within the tissue or organ where they reside, serving as a repair system to replace lost or damaged cells as needed(40).

Stem cells have a wide range of applications in medicine, including treating diseases like spinal cord injury and diabetes (42), potentially growing replacement organs for transplants, aiding in drug development and toxicity testing through 3D cell cultures, modeling human diseases for research, enabling personalized medicine with patient-specific cell lines, regenerating damaged tissues and organs, enhancing cancer treatment effectiveness, developing treatments for genetic disorders, and utilizing stem cell engineering techniques like gene editing and tissue engineering. The versatility and potential of stem cells offer promising avenues for improving healthcare through regenerative medicine and innovative treatments (43).

According to your statement, the model estimated that there were 8.4 million prevalent cases of T1D in 2021, with 1.5 million (18%) of these cases occurring in individuals under the age of 20 (44). Exogenous insulin is administered externally to supplement or replace the body's natural insulin production in individuals with diabetes. It mimics the normal pattern of insulin

secretion, regulating glucose levels by suppressing hepatic glucose production and lowering postprandial blood sugar (45).Despite the availability of traditional treatments such as exogenous insulin therapy, these methods can only alleviate the symptoms but cannot cure diabetes completely (11, 12). The disease has a significant impact on patients' daily life, requiring constant monitoring of medication side effects and imposing a heavy financial burden on individuals, their families, and society as a whole (12).

Exogenous insulin and oral hypoglycemic drugs used in the treatment of diabetes mellitus (DM) can cause various side effects. These include the common occurrence of hypoglycemia, which can be severe and life-threatening. Gastrointestinal issues like nausea, vomiting, and diarrhea may occur with certain oral hypoglycemic drugs (46).There for insulin therapy can be associated with several side effects, including hypoglycemia, weight gain, and insulin resistance. Hypoglycemia is a common side effect of insulin therapy, particularly when insulin doses are too high or when patients do not eat enough food (47). Weight gain is also a common side effect of insulin therapy, particularly when patients are treated with basal insulin analogs, which have been shown to increase the risk of weight gain(48). Insulin resistance can also develop over time, particularly when patients are treated with high doses of insulin, leading to a decreased response to insulin therapy and the need for higher doses to achieve glycemic control (47)

They often focus on symptom control and blood sugar regulation rather than addressing the underlying causes of the disease. This is where stem cells come into play as a promising avenue for regenerative treatments. Stem cells are promising as new regenerative therapies. This regenerative potential makes them a potential tool for replacing damaged or dysfunctional cells and promoting tissue repair (49).

3.3. Stem Cells in Treatment of Diabetes

Transplantation of insulin-producing cells paved the way for stem cell-based regeneration of insulin-secreting pancreatic β-cells. Stem cells are unspecialized and have the potential to self-renew and differentiate into specialized cells such as myocytes, hepatocytes, leukocytes, lymphocytes, erythrocytes, muscles, and neurons under appropriate environmental conditions and signaling(50).The differentiation of stem cells into specific cell types, such as insulin-producing cells for Type 1 diabetes therapy, is a complex process that involves the use of specific growth factors and chemicals to guide the differentiation process (49).

Mesenchymal stem cells (MSCs) possess the remarkable ability to differentiate into specialized cell types either spontaneously or with the aid of chemicals and growth factors.Spontaneous differentiation of MSCs refers to their ability to differentiate into

specific cell types without the addition of specific chemicals or growth factors(51). By utilizing a combination of glucose-rich medium, growth factors, and activation factors, MSCs can be directed to differentiate into insulin-producing cells (IPCs), offering potential therapeutic applications for conditions like diabetes(52).

Embryonic stem cell therapy for Type1 diabetes is a promising approach that involves the use of embryonic stem cells (ESCs) to differentiate into insulin-producing cells, which can help regulate blood sugar levels in patients with Type 1 diabetes. The process of differentiating ESCs into insulin-producing cells is complex and involves the use of specific growth factors and chemicals to guide the differentiation process (53).For example In a study, human embryonic stem cells (ESCs) were differentiated into definitive endoderm by incubating them with a medium containing activin A and Insulin-like growth factor 1 (IGF-1) for 12 days (54). Another study showed that ESCs, when exposed to a medium supplemented with activin A, nicotinamide, and IGF-II for 14 days, differentiated into pancreatic progenitor cells, which are precursors to insulin-producing cells. It is dependindg on mediumcontaing and differentiation day(55).

Induced pluripotent stem cells (iPSCs) are also differentiated through chemical means. iPSCs are adult cells that are reprogrammed to behave like ESCs, and they can be differentiated into various cell types, including insulin-producing cells, using specific growth factors and chemicals (56).

Research has demonstrated that hematopoietic stem cells (HSCs) can be chemically induced to differentiate into insulin-producing cells, offering potential therapeutic applications for diabetes (57).The differentiation of human pluripotent stem cells (hPSCs) into pancreatic β cells, crucial for diabetes treatment, involves the use of various chemicals and growth factors. For example Pancreatic and Duodenal Homeobox 1(PDX1) and NK6 homeobox 1(NKX6.1) transcription factors that play critical roles in the development and function of the pancreas, including the production of insulin (58).

3.4. Some Types of Stem Cells Used in T1DM Therapy

- ✓ Mesenchymal stem cells (MSCs)
- ✓ Embryonic stem cell therapy
- ✓ Induced pluripotent stem cells
- ✓ Hematopoietic stem cells

3.5. Current Advancements and Mechanisms of Stem Cell Therapyin T1DM

3.5.1. Mesenchymal stem cells

Mesenchymal stem cells (MSCs) are a type of adult stem cells found in various body tissues, such as bone marrow, adipose tissue (adipose tissue), and umbilical cord tissue. These cells have the ability to differentiate into different cell types and have immunomodulatory and regenerative properties(27).Treating type 1 diabetes, MSCs have shown potential in several ways:

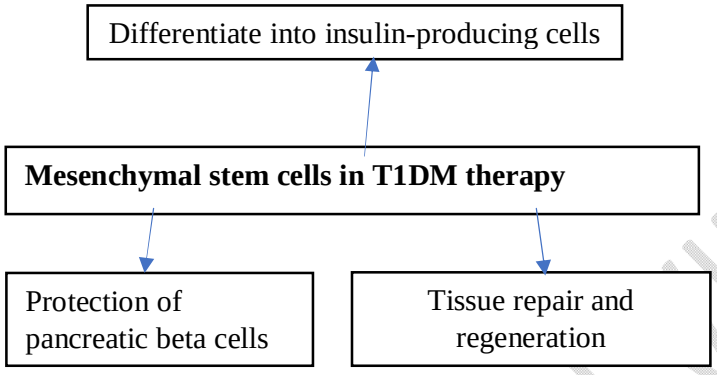


Figure 2. Mechanisms of Mesenchymal stem cells in T1DM therapy

Insulin secretion and pancreatic function

MSCs have the ability to differentiate into insulin-producing cells, similar to pancreatic beta cells. This characteristic makes them valuable in regenerative medicine approaches for diabetes. By transplanting MSCs or promoting their differentiation into insulin-producing cells, it may be possible to enhance insulin secretion and improve pancreatic function asindicated in figure 2 (59).

Protection of pancreatic beta cells

MSCs have been shown to have protective effects on pancreatic beta cells, which are responsible for producing insulin. They can help prevent beta cell apoptosis (cell death) and promote their survival. Preserving and enhancing the function of beta cells is crucial in managing type 1 diabetes(60).

Tissue repair and regeneration

MSCs have regenerative properties and can contribute to tissue repair. In the case of type1 diabetes, they may aid in repairing damaged pancreatic tissue and restoring its normal function. By promoting tissue regeneration, MSCs offer a potential therapeutic approach for treating the underlying causes of the disease(42).

3.5.2. Embryonic stem cell therapy in Type1diabetics

Embryonic stem cells (ESCs) are a type of pluripotent stem cells that originate from the inner cell mass of a developing embryo at the blastocyst stage, usually about 3 to 5 days after fertilization. These cells have a remarkable ability to differentiate into any cell type in the

body, giving them enormous potential in regenerative medicine and research(37). Therefor use of embryonic stem cells (ESCs) in type 1 diabetes mellitus (T1DM) therapy is an area of ongoing research, and the exact mechanisms are still being explored. However, several potential mechanisms have been proposed(61). Here are some of the mechanisms of Embryonic stem cell therapy in Type1 diabeteics:

Differentiation into pancreatic beta cells

ESCs have the ability to differentiate into various cell types, including pancreatic beta cells. Beta cells are responsible for producing and secreting insulin, which is crucial for glucose regulation. By differentiating into functional beta cells, ESCs could potentially replenish the beta cell population in individuals with T1DM, leading to improved insulin production and glucose control (62).

Human embryonic stem cells (hESC) therapy is a new approach to its treatment. hESCs can generate an unlimited number of pancreatic islet cells and are easy to transplant. When cultured directly from endodermal tissues, they differentiated into pancreatic progenitor cells, further leading to the generation of mature pancreatic endocrine cells in vivo. They have a lower chance of immune-mediated rejection (63).

3.5.3. Induced pluripotent stem cells

Potential for Disease Modeling and Drug Screening

IPSCs generated from patients with T1DM can be used to create disease models, enabling researchers to study the disease mechanisms and identify new therapeutic targets. iPSC-derived cells, including beta cells, can also be utilized for drug screening and testing the efficacy of potential anti-diabetic drugs (64).

Insulin-Producing Beta Cells Restoration

IPSCs can be differentiated into insulin-producing beta cells, which are often impaired in individuals with T2DM. The transplanted iPSC-derived beta cells aim to restore or incrse the insulin-producing capacity of the pancreas, thus improving glycemic control (65).

Replacement of dysfunctional or damaged beta cells

In individuals with T1DM, beta cells in the pancreas, which are responsible for producing and secreting insulin, often become dysfunctional (66). They lose their ability to respond adequately to glucose levels in the blood. Therefor iPSC-derived beta cells have the potential to replace dysfunctional or damaged beta cells in the pancreas, addressing the underlying cause of T1DM. These cells can secrete insulin in response to glucose levels, helping to regulate blood sugar levels (66).

3.5.4. Hematopoietic stem cells

Hematopoietic stem cells (HSC) are a type of adult stem cell found mostly in the bone marrow and in small amounts in the peripheral blood (67). These cells have a remarkable ability to self-renew, which means they can divide and produce more identical stem cells and differentiate into different types of blood cells.HSC give rise to all mature blood cells in the body, including red blood cells (RBCs), white blood cells (leukocytes) and platelets. The process by which HSCs differentiate into these specialized cells is called hematopoiesis (67).

Repair Microvascular organs

T1DM can lead to damage to the small blood vessels (microvasculature) in various organs, including the eyes, kidneys, and nerves. Hematopoietic stem cell therapy has shown promise in promoting microvascular repair and regeneration, potentially improving the complications associated with T1DM (68).

Regeneration of beta cells

Some studies suggest that HSCT may stimulate the regeneration of beta cells or improve the function of existing beta cells by improving insulin production and glucose control. pancreatic beta cells are responsible for producing insulin, which is essential for regulating blood sugar (69).

Immunomodulation

HSCT may modulate the immune system, particularly the autoimmune response associated with T1DM. It is thought that the transplantation of hematopoietic stem cells can reset the immune system, leading to a reduction in inflammation and improved regulation of glucose metabolism(70).

3.6. Sourcesof Stem Cell Transplantation

Stem cell transplantation is typically categorized based on the source of the stem cells like autografts, allografts, syngeneic grafts, or xenografts. This means that instead of classifying stem cell transplants based on whether the cells are from the patient themselves (autologous), a genetically matched donor (allogeneic), an identical twin (syngeneic), or a different species (xenogeneic), the focus is on the origin of the stem cells(71).

Autologous transplants use the patient's own stem cells Autologous transplantation eliminates the risk of graft rejection since the stem cells are genetically identical to the recipient(72).**Allogeneic** refers to cells, tissues, or genetic material derived from individuals of the same species but with different genetic backgrounds. The use of allogeneic cells or tissues can provide therapeutic benefits, but managing the immune response to prevent rejection is a significant challenge in these contexts(72).**Syngeneic** transplants use stem cells from an identical twin Since the donor and recipient are genetically identical, there is no risk

of graft rejection(71).**Xenogeneic** transplants transfer stem cells between different species. The classification based on the source of stem cells provides a clearer understanding of the transplantation process and the compatibility considerations involved. This type of transplantation is highly experimental and not widely practiced in clinical settings. Xenogeneic transplantation faces significant immunological challenges due to the differences between species, leading to a high risk of rejection and immune responses(73).

3.7. Preclinical and Clinical Studies ofStem Cells

3.7.1. Preclinical study

Preclinical stem cell therapy refers to the research and testing that occurs before clinical trials in humans. In this phase, researchers are conducting studies to evaluate the potential of stem cell-based therapies for various diseases(29). These preclinical studies are necessary to establish the safety and effectiveness of stem cell therapies before they can be tested in humans. By conducting experiments in vitro and in vivo, researchers try to gather scientific evidence to support the effectiveness of these treatments, laying the groundwork for future clinical trials as described in **Table 1** below (74).Here are below the main procedures for preclinicalstudies:

In Vitro Experiments

Researchers conduct preliminary experiments in a laboratory setting using stem cells to determine their potential to treat a particular disease. This involves testing the ability of cells to differentiate into a desired cell type and assessing their functionality (74).In vitro experiments, which are conducted in laboratory settings using stem cells to evaluate their potential for treating specific diseases, often involve the use of various chemicals to enhance the experiments. One common chemical used to enhance in vitro experiments with stem cells is retinoic acid. Retinoic acid is known for its role in promoting the differentiation of stem cells into specific cell types, making it a valuable tool in studying stem cell behavior and functionality in a controlled laboratory environment (75).

Animal Studies

Preclinical studies typically involve testing the safety and efficacy of stem cell therapies in animal models that mimic the disease being targeted. These studies help evaluate the treatment's effectiveness, potential side effects, and optimal dosage or delivery methods. Researchers monitor the animals' health, perform various tests, and collect data for analysis (76). Animal models, including large animal species like rabbits, dogs, pigs, sheep, goats, and non-human primates, are increasingly important in regenerative medicine and tissue engineering. They bridge the gap between rodent preclinical studies and human clinical trials,

offering a more realistic reflection of human physiology and disease conditions to test stem cell therapies (76).

Safety Assessments

The field of stem cell therapeutics is progressing towards clinical application, but balancing risk and benefit is challenging. Safety issues and gaps in scientific knowledge must be addressed to minimize risk and ensure patient access. Utilizing advanced science, robust assays, and open discussions with regulators is crucial for safe development of stem cell therapies. Preclinical studies focus on assessing the safety of the stem cell therapy. Researchers examine factors such as potential adverse effects, immune response, tumor formation, and the integration of transplanted cells into the host tissue (77).

Optimization

On the base of findings from in vitro and animal studies, researchers refine the stem cell therapy approach, making adjustments to the cell type, dosage, delivery method, and supportive treatments if necessary. This process aims to enhance the therapeutic potential of stem cell therapy by optimizing various parameters based on research outcomes (78)

Regulatory Approval

Regulatory authorities are government agencies or organizations responsible for overseeing and regulating various aspects of healthcare and medical research. Before moving to clinical trials, researchers submit their preclinical data to regulatory authorities to obtain necessary approvals and ensure compliance with ethical and safety standards (79).

3.7.2. Clinical studies

Stem cell therapy clinical trials refer to studies conducted in humans to evaluate the safety, efficacy, and potential therapeutic benefits of using stem cells in the treatment of specific diseases, injuries, or illnesses. These studies are designed to collect data and evaluate the effects of stem cell therapy in a supervised and controlled clinical setting (29).Clinical trials are studies designed to evaluate whether a proposed new therapy or medication is safe and effective. New drugs must undergo clinical trials. Clinical trials are usually divided into four phases (phase I, II, III and IV) clearly described in the **Table 1**(80, 81).

Phase 1

The first phase of clinical trials involves a small number of healthy volunteers or patients with a disease. The main goal is to evaluate the safety of stem cell therapy, determine the appropriate dose and assess possible side effects. The researchers will closely monitor the participants and collect information about the safety profile of the therapy (81).

Phase II

The drug or therapy is given to a larger group of people to test its effectiveness and further assess its safety. In this phase, the focus shifts to evaluating the therapy's effectiveness. A larger group of patients with the disease is enrolled, and researchers assess the treatment's impact on specific outcome measures. This phase helps determine the therapy's efficacy, optimal dosage, and potential side effects in a broader patient population(81).

Phase III

The drug or treatment is given to large groups of people to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect data that allows the drug or treatment to be used safely(81).

Phase IV

Studies are conducted after the drug or treatment is on the market to learn about how the drug works in different populations and about side effects associated with long-term use. Also known as post-marketing or post-approval studies, these are conducted after a drug or treatment has received regulatory approval and is available on the market for clinical use. The main purpose of phase IV studies is to gather more information about the effect, safety profile and effectiveness of the drug in real settings, especially in different population groups and over a longer period of time (81).

Table 1. Preclinical and clinical study description

Study Phase	Key Elements	Description
Preclinical Study	**Purpose**	Research and trials have been conducted before human trials to evaluate stem cell treatments for various diseases. It creates safety and efficiency.
	Invitro experiments	Laboratory tests to assess stem cell differentiation and function for disease treatment. Retinoic acid is used to promote cell differentiation.
	Animal studies	Testing by animal models to assess safety, efficacy, dosage, and side effects. Large animals like pigs and non-human primates offer insight into human uses.
	Safety assessment	Immune response, side effects, carcinogenicity and the incorporation of cells into host tissue are evaluated for safe clinical transplantation.
	Optimization	Refines therapy parameters (e.g., cell type, dosage,

		delivery) based on in vitro and animal data to enhance therapeutic potential.
	Regulatory Approval	Provide real data to regulatory authorities to meet ethical and safety standards prior to clinical trials.
Clinical studies	**Purpose**	Human trials to assess the safety, efficacy, and therapeutic benefits of stem cell therapies under controlled conditions.
	Phase □	A small group study (healthy or sick) to evaluate the safety, dosage and side effects of the treatment.
	Phase □	Larger patient group study to test effectiveness and refine safety data; evaluates impact on outcome measures, dosage, and side effects.
	Phase □	Patient trials to confirm efficacy, monitor side effects and compare with existing treatments to support regulatory approval.
	Phase □	Post-marketing studies to collect long-term data on safety, efficacy and effectiveness in different populations in different parts of the world.

3.8. Case Study of Stem Cell Therapy in Type1 Diabetic Treatments

Stem cell therapy has shown significant promise in treating Type 1 Diabetes, with studies demonstrating its potential to reduce blood glucose levels, improve quality of life, and reduce secondary side effects associated with high blood sugar. Researchers have explored the use of various stem cell types, including bone marrow-derived stem cells, amniotic stem cells, and human embryonic stem cells, in managing the disease. A recent study presented results of three diabetic patients treated with human embryonic stem cell therapy, exhibiting these encouraging outcomes(82).

Another study focused on intrapancreatic autologous stem cell therapy for Type 1 diabetes, where stem cells were implanted directly into the pancreas through the arterial blood supply. This innovative approach demonstrated positive outcomes in terms of symptoms, insulin requirement, blood sugar levels, and autoimmunity (83). Additionally, research has highlighted the potential of stem cell therapy in generating insulin-producing cells from various stem cell sources, offering a novel approach to managing Type 1 diabetes (84)

Table 2. Use of Stem Cells in the Treatment of Diabetes Mellitus: A Case Series(83)(84).

Study	Stem Cell Type	Treatment Approach	Outcomes
Study 1	Human Embryonic Stem Cells	Blood glucose reduction, reduced secondary side effects of high blood sugar	Improved quality of life
Study 2	Autologous Bone Marrow-Derived Stem Cells	Direct implantation into the pancreas through arterial blood supply	Positive effects on symptoms, insulin requirement, blood sugar levels, and autoimmunity
Study 3	Various Stem Cell Sources	Generation of insulin-producing cells	Potential for novel diabetes management

The studies collectively demonstrate the potential of stem cell therapy in revolutionizing the treatment of Type 1 diabetes, offering hope for improved outcomes and quality of life for patients as described in **Table 2**(84)

In other study over 5 years, 21 patients with Type 1 diabetes received autologous stem cell therapy involving transplantation into the Omental pouch, peritoneum, and blood, while 26 controls received insulin injections. The therapy group showed significant improvements in weight gain, reduced insulin requirements, decreased HbA1c, and increased C-peptide levels, not seen in controls, with only mild temporary side effects as described in **Table 3**below(85).

Table 3. Autologous stem cell therapy in treatment of type1 diabetes(85)

Average weight gain after 1 year	Statistically significant as indicated below	Not statistically significant
Daily insulin requirement	Decreased significantly	No significant change
HbA1c levels	Decreased significantly	No significant change
Fasting and postprandial blood	Decreased significantly	No significant change

sugar		
C-peptide levels	Increased significantly	No significant change
Anti-GAD antibody titer	Decreased significantly	No significant change

Table 3 indicts autologous stem cell therapy involving transplantation into the Omental pouch, peritoneum, and blood showed safety and long-term efficacy in treating Type 1 diabetes, with the therapy group demonstrating statistically significant improvements compared to controls. Further research with larger samples and longer follow-up is needed to optimize this promising approach that offers hope for Type 1 diabetes patients(83)

4. CHALLENGES STEM CELL THERAPY IN T1 DMTREATMENT

Stem cell therapy holds promise in the treatment of diabetes mellitus (DM) by utilizing for example mesenchymal stem cells (MSCs) due to their differentiation potential, immunosuppressive properties, and anti-inflammatory effects(86). Despite the exciting therapeutic effects demonstrated in glycemic control both in vivo and in vitro, there are critical challenges associated with stem cell therapy for DM(42). Here are below some challenges of stem cell therapy in diabetic treatment:

Scale up issues: After optimizing the right development steps, scaling issues arise.Obtaining a sufficient number of cells for therapy can be challenging. Thus, there is a need for effective techniques to maximize yield while accommodating land use requirements. To maintain a balance between demand and utilization, the scaling potential of stem cells must be further explored to provide additional supplies of transplanted cells(87).

Tumorigenicity and Abnormal Cell Growth: Stem cells have the potential for uncontrolled growth, leading to the formation of tumors or abnormal cell growth after transplantation. Addressing this challenge involves refining protocols and conducting thorough safety evaluations to minimize the risk of tumorigenicity(88).

Immune Response and Rejection: Transplanted stem cells or derived beta cells face the risk of immune rejection by the recipient's immune system. Overcoming this challenge requires developing effective immune modulation strategies to prevent rejection and maintain long-term graft survival(87).

Safety and Efficacy: Ensuring the safety, reliability, and long-term efficacy of stem cell therapy, including addressing issues like tumor formation, untargeted differentiation, and autoimmunity, is crucial for successful treatment outcomes(89).

Ethical Concerns: The use of embryonic stem cells raises ethical issues, while induced pluripotent stem cells face challenges related to differentiation efficiency, stability, and cost (87).

Limited Differentiation Potential: Adult stem cells have a restricted differentiation capacity, which may limit their effectiveness in generating insulin-secreting cells for T2DM treatment. Adult stem cells are undifferentiated cells found in various tissues in the body, such as bone marrow or adipose tissue. They have self-renew and differentiate into some, but not all, cell types of the tissue from which they originate (40).

5. DISCUSSION

The classical treatment for type 1 diabetes involves lifelong insulin therapy, which aims to maintain blood glucose levels within the normal range (17). Patients with type 1 diabetes require exogenous insulin administration to regulate glucose homeostasis, as their pancreatic beta cells are unable to produce sufficient insulin due to autoimmune destruction (90). While insulin therapy has been the mainstay of treatment for type 1 diabetes, it is not without its limitations and side effects. Inaccurate insulin delivery can lead to lack of glycemic control and potentially life-threatening hypoglycemia(17). Furthermore, insulin therapy does not prevent the development of microvascular complications, such as nephropathy, neuropathy, and retinopathy, which can significantly impact the quality of life for patients with type 1 diabetes(90).

In recent years, stem cell therapy has emerged as a promising alternative approach for treating type 1 diabetes. The goal of stem cell therapy is to replace the damaged insulin-producing beta cells with functional cells derived from stem cells, thereby restoring insulin production and potentially curing the disease(91). Several studies have demonstrated the potential of Several types of stem cells have been investigated for their potential in treating type 1 diabetes, including embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), and mesenchymal stem cells (MSCs)(17). These stem cells can be differentiated into insulin-producing cells and transplanted into patients with type 1 diabetes(91). Stem cell therapy offers several advantages over classical insulin therapy. By providing a renewable source of insulin-producing cells, stem cell therapy has the potential to eliminate the need for exogenous insulin administration and prevent the development of diabetes-related complications(90).

Additionally, some studies have suggested that stem cells may possess immunomodulatory properties, which could help control the autoimmune response responsible for the destruction of pancreatic beta cells. However, stem cell therapy for type 1 diabetes is still in the

experimental and clinical trial stages(92). Challenges remain, such as optimizing the differentiation protocols to generate mature, functional beta cells, ensuring long-term survival and function of the transplanted cells, and preventing immune rejection without the need for lifelong immunosuppression(17). Despite these challenges, the potential of stem cell therapy to revolutionize the treatment of type 1 diabetes is promising. As research continues and clinical trials progress, stem cell therapy may one day become a viable alternative to classical insulin therapy, offering patients with type 1 diabetes a chance at a functional cure and improved quality of life(17).

6. CONCLUSION

Stem Cell Therapy for Type 1 Diabetes" highlights the advances and opportunities in the use of stem cells in the treatment of type 1 diabetes. Stem Cell Therapy in Type 1 Diabetic Treatment shows significant potential as a safe and effective approach to managing T1D. While current advancements have demonstrated positive outcomes, future research should focus on addressing challenges, refining treatment protocols, and conducting larger-scale studies to establish the long-term efficacy and safety of stem cell therapy for T1D.Studies show the successful differentiation of stem cells into functional beta cells, which promises better glucose balance and reduced insulin dependence. Challenges like as immune rejection and tumorigenicity will be addressed, and future focus will be on individualized medical approaches and optimizing the functionality of stem cell beta cells

7. FUTURE PROSPECTIVE

Based on the conclusion here are below main points of future prospective:

Possibility for Improved Glycemic Control: For example MSCs have shown promising results in improving glycemic control, reducing the need for daily insulin, and enhancing the function of pancreatic islets. The presentation explores the potential of stem cells in not only replacing damaged pancreatic cells but also modulating the immune system to prevent further destruction of insulin-producing cells near future, which could lead to better management of DM (42).

Research Advancements: Ongoing research is focusing on enhancing the differentiation of stem cells into insulin-producing cells, which could lead to more efficient and targeted therapies for DM.(93)

Alternative Treatment Option: Stem cell therapy offers a novel approach to treating DM by addressing insulin resistance and dysfunction of insulin-producing beta cells, potentially providing a more effective and long-lasting treatment strategy (87)

Standardization and Scalability: Establishing standardized protocols for stem cell production, differentiation, and transfer is critical to making stem cell therapies feasible on a larger scale. Achieving reproducibility and scalability ensures consistent quality and wider availability of care (94).There for I hope Stem Cell Therapy as a Game-Changer in Diabetes Treatment in Ethiopia.

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