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# Stem Cells and Diabetes: A New Era of Regenerative Medicine

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**Abstract: Diabetes is a chronic metabolic disorder and is recognized as the most common condition affecting the endocrine system. It is characterized by high blood sugar levels due to insulin resistance, insufficient insulin production, or a combination of both. This condition is often associated with various acute and chronic complications. Managing these complications has placed a considerable financial burden on many communities. Over the past decade, pancreatic islet transplantation has been thoroughly investigated as a potential treatment for diabetes. However, obtaining pancreatic cells from cadavers is quite difficult due to inherent limitations. Stem cells are being explored as a renewable cellular resource that could serve as an alternative to organ transplantation. These cells, found in nearly all multicellular organisms, have the unique ability to divide and differentiate into specialized cells, as well as to regenerate damaged or missing cells. The scientific community has extensively considered the potential application of stem cells in treating diabetes and developing insulin-producing islets, which may offer a promising future solution for diabetes management. Notably, human stem cells derived from hematopoietic organs, liver, pancreas, and embryonic sources are among the various types being studied. This article provides a brief overview of a series of research efforts conducted in this area.**

***Keywords:*** *Diabetes, Insulin Resistance, Pancreatic Islet Transplantation, Organ Transplantation Alternative, Stem Cells, Hematopoietic Stem Cells, Pancreatic Islet Transplantation*

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## I. INTRODUCTION

Diabetes is a condition that alters an individual's metabolism, characterized by chronic hyperglycemia which results either from a defect in insulin secretion or action or both such patients. The human organism produces insulin which is a hormone manufactured by the pancreas. It takes up glucose from the blood and helps transform it into energy for various cells in the body. In diabetes patients, insulin hormones are either lacking or present but unsuitable for a number of reasons, thus making it impossible for the body cells to adequately uptake glucose from the blood for several of its needs. As a result, there is a gradual increase in the amount of sugar or glucose contained in the bloodstream, which can cause damage to the body's organs over a period of time. Type II diabetes is considered to be one of the most frequent non transmissible diseases around the world, and is frequently the main cause of mortality in several nations [1]. Diabetes mellitus is the main factor for blindness in individuals aged between 25 to 75 years and also a major cause for limb amputation as well in the United States due to its great effect related. In addition to that, diabetes is a disease that affects 35% of dialysis patients with end-stage renal disease. There is a relationship between the higher increasing rates of prevalence and the demographic's aging with modification of lifestyles, effective economic development and increase of obesity. As reported by a study in 2010, the number of diabetes patients in the Middle East is likely to rise significantly by the year 2030. In addition, it was predicted that in 2030, Iran is expected to have the second annual prevalence of diabetes in the region after Pakistan [2]. Diabetes can be connected to symptoms such as excess peeing, drinking excessively, and eating too much. Additionally, these symptoms are also associated with exhaustion, vision problems, difficulty healing wounds or bruising over time, and weight reduction despite a high intake of calories (which is frequently noticed in Type I diabetes patients), pain and numbness in fingers and toes (seen mostly in Type II diabetes patients who are over the age of 40), feeling drowsy, lack of interest, being overweight and having high cholesterol levels.

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Diabetes is the underlying cause for disorders pertaining to almost all of the organs and is further classified into two categories: early and late complications. There are certain factors leading to the onset of these epidemics, especially, a dramatic transformation in the people's lifestyle. These factors include a sedentary lifestyle and eating unhealthy foods. However, there is a catch associated with type II diabetes in some cases. The majority of its patients have difficulty in identifying its symptoms. If diabetes can be detected at an early stage alongside the timely treatments, the adverse effects related to it can be prevented [3].

## II. TYPES OF DIABETES

The main types of diabetes are Type I and Type II, and the number of people affected by different forms of diabetes is rising around the world. Type II diabetes is much more common than Type I, primarily due to recent changes in lifestyle, the rise in obesity rates, and a decline in physical activity [4]. Type I diabetes is marked by a substantial reduction in insulin levels caused by the destruction of pancreatic beta cells. This occurs due to a process called self-immunity. In contrast, type II diabetes sees a relatively lower production of insulin, which can decrease by approximately 50% [5].

Insulin production is insufficient to counteract insulin resistance in this condition, resulting in decreased insulin secretion in both forms of diabetes. Among individuals with long-standing diabetes, almost 99% showed inadequate beta cell activity in type I diabetes, while in type II diabetes, this figure varied between 40% and 60%. Treatment for Type I diabetes requires daily and frequent insulin injections, whereas Type II diabetes can often be managed with oral medications that target beta cells or peripheral tissues [6]. The ADA and EASD outline five different categories of second-line anti-glycemic medications. These include dipeptidyl peptidase 4 (DPP-4) inhibitors, glucagon-like peptide-1 receptor agonists (GLP-1RA), sodium-glucose cotransporter 2 (SGLT2) inhibitors, sulfonylureas, and thiazolidinediones [7]. Still, none of these therapies completely match the normal biological activity of the Beta cells. They struggle to provide optimal control and to avoid harmful side effects [8]. Maintaining consistent blood sugar levels can lead to a higher occurrence of hypoglycemia in both types of diabetes. In the United States, most diabetic patients receiving treatment for Type I had glycosylated hemoglobin levels exceeding 7.5%. In contrast, the average glycosylated hemoglobin level for Type I patients in Japan was 8.2%, while for those with Type II diabetes, it stood at 7.4%. 4 (Table 1) [9]. Reports indicate that gestational diabetes and other types of diabetes are linked to various conditions. About 3 to 5 percent of pregnant women, especially in the later stages of pregnancy, experience diabetes. Those who are predisposed to diabetes often have several risk factors that increase their chances of developing gestational diabetes. While the condition typically resolves after childbirth, it can reappear in future pregnancies. Around 50% of women who have diabetes during pregnancy go on to develop chronic diabetes. Therefore, it is advisable to inform them about suitable preventative programs for both mothers and their children, under professional guidance. Current research shows that diabetes is not an entirely manageable condition that lasts a lifetime; however, it can be effectively managed through a partnership between the physician and the individual with diabetes, creating a supportive environment that helps prevent a negative self-image [3].

- *Complications of Diabetes*

Diabetes can have serious negative effects on various systems and organs in the body, potentially resulting in a range of early and late complications. This condition can cause disabilities, paralysis, high medical costs, and even death. Additionally, diabetes is linked to complications such as heart problems, kidney disease, nerve damage, eye issues, cataracts, and other health concerns [10].

Table 1 Comparison of two types of diabetes type 1 and 2 [11].

| Aspect | Type 1 Diabetes | Type 2 Diabetes |
|---|---|---|
| Occurrence | Primarily in infants and adolescents (aged under 20) | Mainly in adults aged 40 and older |
| Prevalenc | Minimal (5-10% of diabetes cases) | Elevated (80-85% of diabetes instances) |
| Risk Factors | Genetic susceptibility and autoimmune destruction of beta cells | Genetic predisposition, lifestyle choices, and environmental influences |
| Cause | Destruction of beta cells | Insulin resistance and compromised insulin secretion |
| Insulin Dependency | Synthetic insulin is necessary | Exogenous insulin may be necessary. |
| Ketoacidosis | High risk | Rare occurrence |
| HLA Association | Having a strong link with HLA genes | No HLA association |
| Twin Studies | Predisposition in identical twins more than 50% | >70% likelihood in sets of identical twins |
| Treatment | Insulin treatment, nutritious diet, physical exercise | Insulin, nutritious diet, physical exercise |
| Complications | Diabetes-related ketoacidosis is a potential risk. | The syndrome of hyperosmolar coma is a possibility. |

Diabetic ketoacidosis is a serious complication that primarily occurs in Type I diabetes and, to a lesser extent, in Type II diabetes, especially in certain pathological conditions. It results from either a complete or partial deficiency of insulin. This condition is characterized by three main clinical features: hypoglycemia, ketosis, and acidosis. On the other hand, hyperosmolar coma syndrome complications are more commonly associated with Type II

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diabetes. While the underlying causes of this syndrome are similar to those of diabetic ketoacidosis, it does not present with ketosis or acidosis. Insulin resistance is frequently observed in this syndrome. [2]

Diabetes is the fifth leading cause of death and is primarily responsible for chronic kidney failure, non-traumatic amputations, and blindness in many cases. Recent studies suggest that a healthy diet, regular physical activity, and the management of blood sugar, blood pressure, and cholesterol levels may help reduce the risks associated with diabetes and its complications, such as cardiovascular and kidney problems, as well as eye issues [12].

Diabetic neuropathy is a common complication of diabetes that impacts the peripheral nerves in the body. It is associated with higher mortality rates and increased costs related to diabetes care. This condition typically arises as a late complication of type I diabetes and an early complication of type II diabetes. Delayed diagnosis of diabetes and its related issues significantly contribute to the higher rates of this condition. While the occurrence of neuropathy in individuals with type I diabetes tends to decrease with age, it tends to increase with age in those with type II diabetes. Additionally, diabetic retinopathy is a major chronic eye condition linked to diabetes, resulting in reduced vision and blindness, which can significantly affect social and work productivity worldwide [13].

The availability of thyroid hormones is crucial for maintaining optimal metabolism, as they play a significant role in the processes and pathways that facilitate it. Thyroid hormones primarily influence the metabolism of carbohydrates, proteins, and lipids across all tissues. They can affect metabolic processes such as managing blood lipid levels, lowering cholesterol, and increasing metabolic rate. In diabetic conditions, the secretion of thyroid hormones can change, leading to notable metabolic and enzymatic shifts in cholesterol, phospholipids, and triglycerides. These changes are particularly evident in hypothyroidism, while a decrease is observed in hyperthyroidism. The metabolic changes caused by both thyroid hyperactivity and hypothyroidism can disrupt blood sugar regulation and worsen diabetes. Since the follicles of the thyroid gland are the main source of thyroid hormone release, any changes in hormone secretion can impact the size of the follicles and the overall volume of the thyroid gland at the cellular level, as well as affect the normal functioning of various body cells. As a result, there can be an increase in plasma concentration of thyroid hormones [14,15]. Reducing the impact of insulin on the liver leads to increased gluconeogenesis and glycogenolysis, which is due to heightened hepatic glucose production. A notable rise in triglyceride and cholesterol levels in Type I diabetes, along with an increase in triglycerides in Type II diabetes, suggests lipid issues mainly caused by diabetes or possibly linked to insulin deficiency or resistance [16]. In type I diabetes, there is a significant increase in glucose, triglycerides, and cholesterol levels. At the same time, LDL, HDL, and insulin levels tend to decrease. Many studies have indicated higher triglycerides and cholesterol levels, along with lower LDL and signs of hypothyroidism, implying that people with Type I diabetes may be experiencing hypothyroidism [17]. Compared to the control group, individuals with type II diabetes show significantly higher average levels of insulin and glucose, along with increased triglycerides. In this group, LDL and HDL levels experience a slight decrease, while cholesterol levels remain relatively stable. Both type I and type II diabetes can indirectly affect the structure of the thyroid gland by changing the body's requirement for thyroid hormones [18]. The reduced activity of lipoprotein lipase in people with diabetes results in lower skin fat content, which leads to less moisture being released and causes dry skin. Additionally, a lack of collagen, due to decreased production in diabetic skin, makes the skin more vulnerable to environmental factors. High glucose levels in those with diabetes can also contribute to dryness and fragility, increasing the risk of infections and delaying wound healing. Diabetic foot ulcers are often the result of poor blood sugar control, peripheral vascular disease, nephropathy, and a weakened immune system [19].

- *Treatment of Diabetes*

Managing type I diabetes requires daily and frequent insulin injections, whereas Type II diabetes can often be managed with oral medications that influence the beta cells in peripheral tissues. However, these medications do not completely mimic the normal functioning of beta cells, which can lead to insufficient control and possible side effects. [20] In the United States, most patients with type 1 diabetes who are receiving treatment have a glycosylated hemoglobin level exceeding 7.5%. In Japan, type 1 diabetes patients have an average glycosylated hemoglobin level of 8.2%, while those with type 2 diabetes average 7.4% [21]. Nearly 40 years ago, a successful pancreatic transplant was performed. Since that time, numerous attempts have been made to systematically transplant activated beta cells into patients to restore insulin production in individuals with type I diabetes. Pancreas transplants have been carried out in a small number of patients, especially those who also needed a kidney transplant, primarily due to the associated risks. Moreover, the transplantation of islets of Langerhans has recently attracted significant interest. The first successful transplant occurred in 1999, and later efforts aimed to transfer these islets to the efferent vein of the liver. Some patients who received islets of Langerhans did not require insulin during the initial years; however, over time, the transplanted islets lost their functionality, leading to the need for insulin therapy once again. The key factors contributing to the reduced lifespan of beta cells include the need for immunosuppressive drugs, which are associated with the risk of autoimmune recurrence and side effects, as well as the limited number of available tissue donors, which greatly restricts the widespread application of this technique [22]. Lately, the application of stem cells in treating diabetes has attracted considerable attention. Studies conducted more than 50 years ago revealed that stem cells can divide multiple times while retaining their undifferentiated state. Yet, when they encounter specific stimuli that trigger the production of essential genes, they can differentiate into various specialized cell types. Significant efforts have been made to harness stem cells to replace dysfunctional and cancerous cells in lab research, but only a limited number of clinical trials have been initiated [23]. The limitations in the

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quantity and reproductive capacity of adult stem cells, along with the difficulties in isolating them, have led many researchers to explore the potential of fetal stem cells over the past decade. These cells possess a variety of characteristics and have the ability to replicate themselves. The first experimental studies on this topic were published in 2000. Following that, additional research indicated that embryonic stem cells could be developed into insulin-producing cells, which could help lower elevated blood sugar levels in experimental animals. A significant challenge in using beta cells derived from embryonic stem cells is the risk of rejection by the host organism. This issue has been tackled through the use of immunosuppressive drugs. More recently, advancements in capsule design have improved nutrient exchange while preventing immune cell infiltration, thus supporting the transfer of differentiated cells. In this approach, embryonic stem cells grown in vitro are selected for genetic events that promote growth, such as the replication of c-myc [24].

## III. STEM CELLS

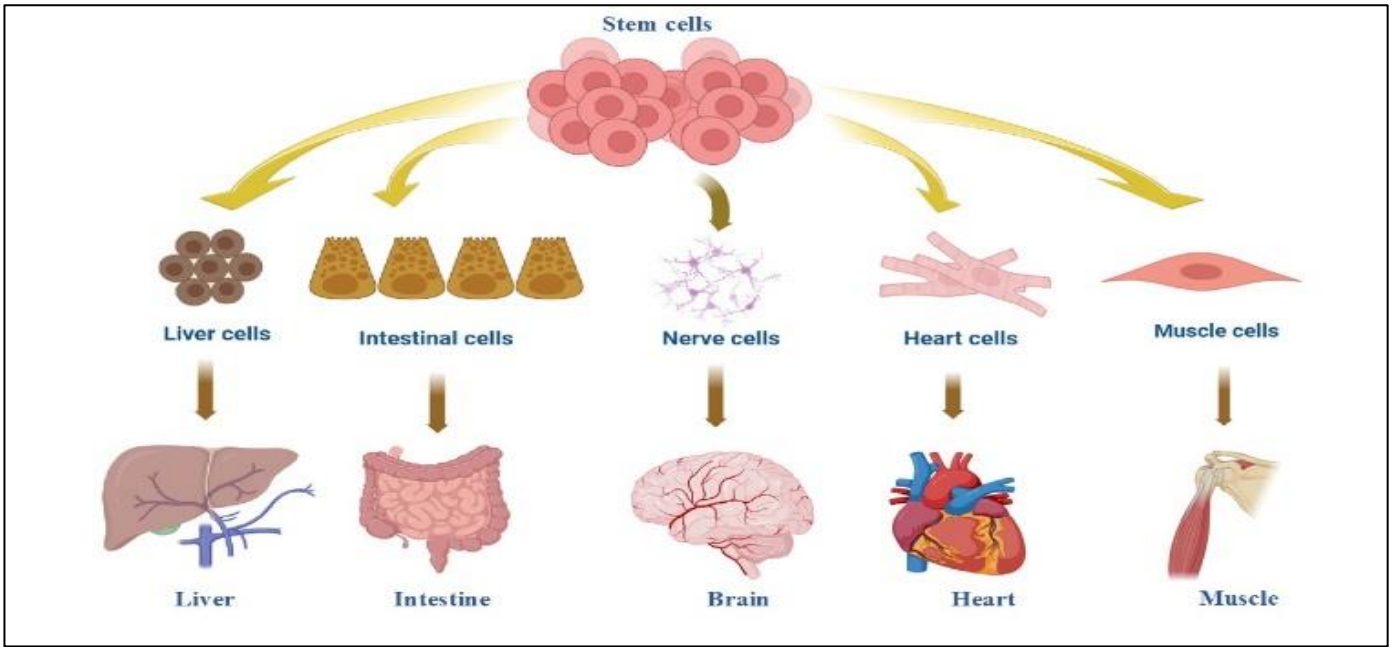


Fig 1 The Importance of Stem Cells for Our Health

Stem cells are characterized by two factors: their ability to undergo self-replication via mitotic divisions to sustain their population and their capacity to specialize into diverse cell types. In the growing embryo, stem cells may differentiate into particular cell types originating from the three primary germ layers: ectoderm, endoderm, and mesoderm. The resultant cells may engage in the regeneration and substitution of some renewable organs, including blood, skin, and digestive tissues [25]. Adult stem cells play a significant role in medical treatments. For instance, bone marrow is rich in stem cells that can grow and transform into specific cell types, resembling various tissues in the body, such as muscle and nerve cells. Pluripotent stem cells have the unique ability to create a fully formed organism, although they can also differentiate into both embryonic and extra-embryonic cells. The cells that arise from the initial divisions of a fertilized egg are considered fully viable. Pluripotent stem cells, which come from pluripotent cells, can develop into all types of embryonic cells. In simpler terms, they produce all the cells that come from the embryonic germ layer. On the other hand, multipotent stem cells can only develop into cell types that are specific to their original germ layer, while unipotent stem cells are limited to generating cells that are very similar to themselves [26].

- *Types of Stem Cells*

Mammals primarily have two types of stem cells: embryonic stem cells, which come from the inner cell mass of the blastocyst, and adult stem cells, found in mature tissues and serving as the body's repair system. The embryonic stem cells from the inner cell mass of the blastocyst are known for their regenerative abilities. About 4 to 5 days after fertilization, the human embryo reaches the blastocyst stage. These cells are so versatile that, when given the right signals, they can develop into various cell types present in an adult organism. This versatility also means they can form teratomas, which are unusual tumors that may contain immature or fully developed tissues like teeth, hair, bone, and muscle.

Importantly, these cells cannot differentiate into extra-embryonic cells. Embryonic stem cells are characterized by specific transcription factors and unique cell surface proteins. By inhibiting certain differentiated genes, these factors have become the main regulators of embryonic stem cell pluripotency [27].

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➢ *Embryonic Stem Cells*

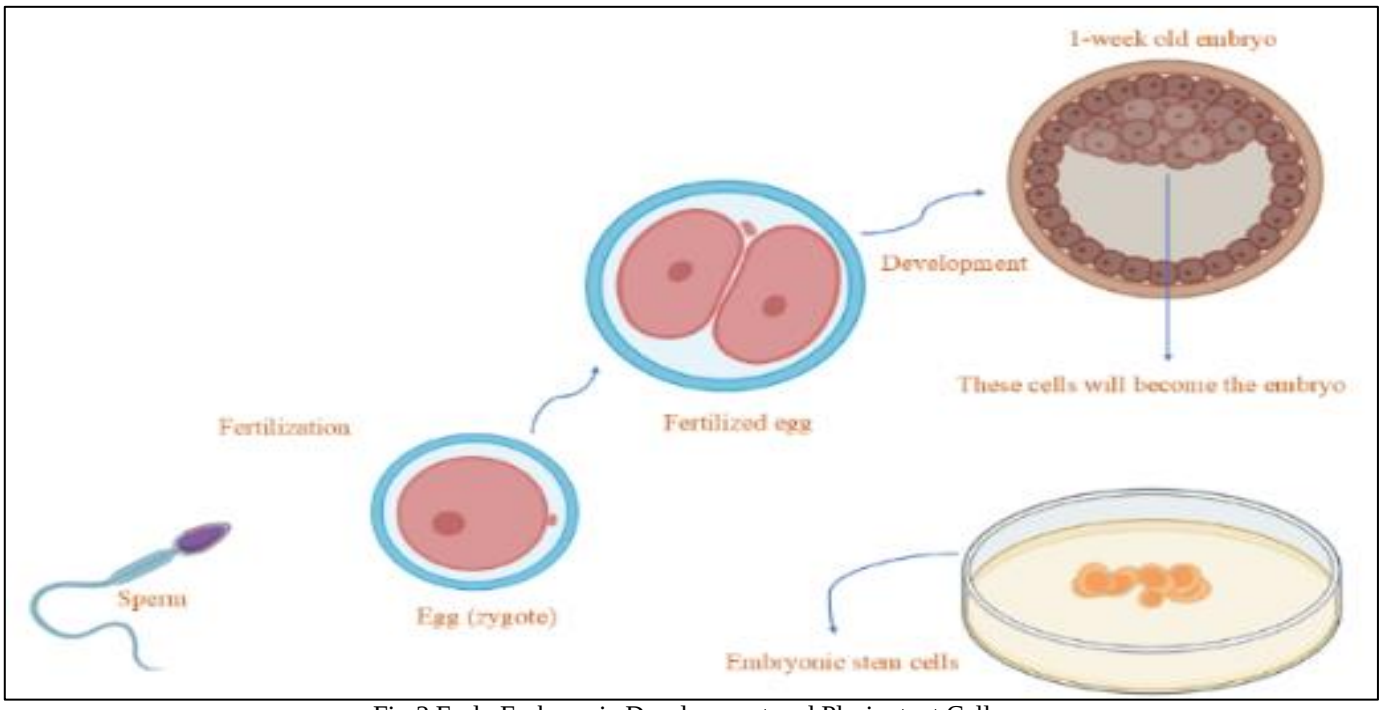


Fig 2 Early Embryonic Development and Pluripotent Cells.

Embryonic stem cells are undifferentiated stem cells located in many organs of the fetus. There are two categories of embryonic stem cells. Fetal-specific stem cells, derived from the tissues of aborted fetuses, are not eternal; rather, they possess significant proliferative capacity and are multipotent. Extraembryonic stem cells, which come from extraembryonic membranes, are similar to adult stem cells. They can be obtained after birth and have remarkable abilities for cell division and pluripotency. Multipotent stem cells can be found in amniotic fluid. Although they are highly active, they do not have the potential to cause cancer, but they can differentiate into fat, bone, muscle, liver, and nerve cells [28].

Mesenchymal cells obtained from umbilical cord blood are multipotent, yet they do not show the markers typically linked to blood cell lineages. Two key features of these cells are their low immunogenicity, which is mainly indicated by a decreased production of MHC antigens, and their lack of stimulation in the growth of allergic lymphocytes. These mesenchymal cells can differentiate into various mesenchymal tissues, such as bone marrow, cartilage, muscle, tendon, and adipose tissue [29].

➢ *Mature Stem Cells*

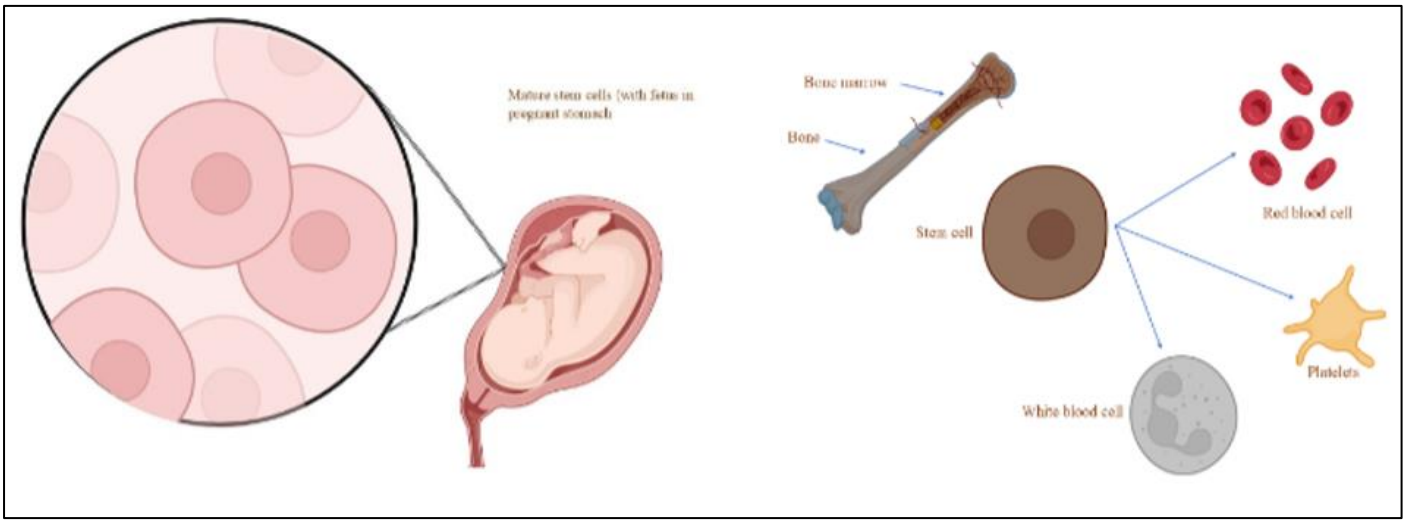


Fig 3 Mature Stem Cells

Adult stem cells, also known as somatic stem cells, play a crucial role in the maintenance and repair of tissues. They can be found in both children and adults. Some rare adult pluripotent stem cells exist in limited amounts in

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umbilical cord blood and similar organs. Bone marrow is a rich source of adult stem cells, frequently utilized in various scientific research. The number of mature bone marrow stem cells decreases with age, and interestingly, men tend to have more than women during their reproductive years. Most adult stem cells are multipotent and are typically identified by the tissue from which they originate. Importantly, obtaining these cells does not require the use of embryos, thus avoiding the associated ethical issues. Additionally, while these cells can be used as autografts, they do not carry a risk of tissue rejection [27].

Bone marrow stem cells: Bone marrow serves as the primary source of adult stem cells. There are two primary categories of stem cells inside the bone. Marrow: (1) Bone marrow stem cells, which serve as the initial progenitors of blood cells, differentiating into all varieties of blood cells, including both myeloid and lymphoid lineages.Bone marrow stromal stem cells, also known as mesenchymal stem cells, are non-hematopoietic cells found in the bone marrow. These multipotent stem cells have the ability to differentiate into various cell types in both laboratory settings and physiological conditions [30]. In addition to bone marrow, there are other sources known as tissue-specific mesenchymal stem cells. These sources are utilized for obtaining mesenchymal stem cells. Some mesenchymal stem cells can be sourced from adipose tissue, skeletal muscle, and deciduous teeth. Mature stem cells derived from adipose tissue are often extracted by liposuction. This group of cells seems to be very similar to mesenchymal stem cells derived from bone marrow. In the laboratory, they can develop into bone, cartilage, adipose tissue, muscle, and maybe nerve tissue. [31] Neural stem cells are known to be primarily found in the lateral ventricles of the brain and the dentate gyrus [32].

Human olfactory mucosa cells serve as the parent cells that give rise to mature olfactory stem cells. The characteristics and potential of these cells can be influenced by specific chemicals that promote or trigger cell differentiation, leading to the creation of cells with enhanced differentiation abilities [33]. Pluripotent stem cells can be generated directly from adult stem cells, with one type known as induced pluripotent stem cells. This advancement has eliminated the ethical concerns associated with using embryos, meaning patients no longer have to worry about compatibility issues or other complications. The remarkable ability of multipotent cells to proliferate indefinitely makes them a promising avenue in regenerative medicine. They can rapidly differentiate into various cell types within the body, including neurons, heart cells, pancreatic cells, and liver cells, providing a unique resource for repairing or replacing damaged tissues.Induced pluripotent stem cells share many characteristics with natural pluripotent stem cells. These similarities include comparable gene and protein expression, similar chromatin methylation patterns, consistent doubling times, the ability to form embryoid bodies, the development of teratomas, and the capacity to generate viable chimeras [34].

Additionally, these cells have various limitations. Some reprogramming factors can be carcinogenic, and the integration of transcription factors into the genome might pose a risk of causing mutations in the genomes of the target cells.The capacity of stem cells to produce cells that originate from all three embryonic germ layers demonstrates that these cells have the potential to be used in the process of tissue and organ synthesis. This capability has been shown in several studies [35].

- *Stem Cell Transplantation as A Therapeutic Approach for Diabetes*

Induced multipotent cells have sparked significant hope for tissue replacement. However, they have not yet met the need for beta cell replacement and diabetes treatment. To create functional beta cells from either novel or induced stem cells, it is essential to ensure their proper differentiation and to complete the developmental stages that normal beta cells undergo. Additionally, initiating this differentiation requires accurately identifying the transcription factors and small compounds that affect the expression of these factors, metabolic enzymes, or surface transporters. Throughout this process, some genes need to be turned off while others must be turned on. In certain cases, it may be necessary to substitute them with alternative versions delivered through various external vectors, including viruses [36].

The first research exploring the therapeutic benefits of stem cells for treating type 1 diabetes patients took place in Brazil in 2003. Since then, numerous facilities across various countries have begun their clinical studies [37]. A selection of papers examining the benefits of stem cells, as well as the obstacles and advancements in diabetes therapy, is included in Table 2.

- *Studies Focused On Embryonic Stem Cells Originating from Animals*

Rat embryonic stem cells grow in an undifferentiated state when exposed to leukemia inhibitory factors. When the right conditions are created for the differentiation of different cell lines by directing them along specific pathways, they begin to differentiate and develop.

A significant number of studies have focused on the similarities in the evolutionary paths of the pancreas and the central nervous system, initially attempting to differentiate embryonic stem cells into neuronal cells. Following this, researchers sought to create pancreatic islet beta cells by employing genetic modifications and adjusting the culture environment with various growth factors [38]. Significant studies on rats have demonstrated the conversion of embryonic stem cells into insulin-producing cells, as highlighted in previous research that has been extensively cited by various groups. This research utilizes neuron production methods to transform embryonic stem cells into pancreatic cells, highlighting similarities in the developmental regulatory processes of the central nervous system and the pancreas [39].

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Table 2 List of some articles examining stem cells as a treatment for diabetes

| The title of the study | Study type | Overall result | Authors |
|---|---|---|---|
| Stem cell therapy for diabetes: do we need to make beta cells? | Descriptive research analytical | It is quite probable that stem cell transplantation may treat type 1 diabetes. Assuming they retain the functional phenotype of pancreatic beta cells, stem cells provide hope for the eventual production of vast quantities of insulin-producing cells. | [40]. |
| The Potential for Stem Cell Therapy in Diabetes | Descriptive research analytical | Recent advancements in the isolation, culture, and differentiation of embryonic stem (EC) cells have sparked new hope that beta cells could eventually be utilized to treat diabetes, offering a potential alternative to pancreatic transplantation. | [41]. |
| Stem Cell Therapies in Regenerative Medicine and Diabetes Mellitus: Advances, Constraints and Future Prospects | Descriptive research analytical | Pancreatic cells are among the most effective and abundant types of embryonic stem cells. When they develop into insulin-secreting cells and create island-like structures in the laboratory, these cells could potentially aid in the treatment of hyperglycemia. | [42]. |
| Stem Cell Therapy in Diabetes | Descriptive research analytical | Pancreatic cells are among the most effective and abundant types of embryonic stem cells. When they develop into insulin-secreting cells and create island-like structures in the laboratory, these cells could potentially aid in the treatment of hyperglycemia. | [43]. |
| Stem cell therapy for diabetic foot ulcers: a review of preclinical and clinical research | Analytical research | Adipose tissue stem cells migrate to the vascular areas of lesions and wounds in patients with diabetes. They help protect the damaged tissue by promoting the formation of new blood vessels, reducing tissue scarring, and improving oxygen supply to the affected area. | [44]. |
| Stem Cell Therapy: Recent Success and Continuing Progress in Treating Diabetes | Descriptive research analytical | This research concludes that accessing stem cells is the most promising treatment for diabetes. However, the high costs involved in creating, maintaining, and maturing stem cells present considerable challenges to this method. | [45]. |
| Current progress in stem cell therapy for type 1 diabetes mellitus | Analytical research | Stem cell-based therapy is suggested as a promising therapeutic treatment for diabetes, particularly type 1 diabetes. | [46]. |

Monkey embryonic stem cells have been transformed into insulin-producing cells through a process of spontaneous cell differentiation. The growth factor beta-oxendin-4 was utilized to promote cellular differentiation and development. Additionally, C-peptide levels were measured to confirm the synthesis of insulin by the cells derived from embryonic stem cells [47].

- *Advancements in Research On Human Embryonic Stem Cells*

Human embryonic stem cells can develop into insulin-producing cells when placed in the right growth medium. One key difference between human and mouse embryonic stem cells is that the leukemia inhibitory factor encourages the undifferentiated growth of these cells in mice, but it does not significantly affect human embryonic stem cells. For human embryonic stem cells to grow undifferentiated, they need to be placed on a layer of feeder cells. When human embryonic stem cells are placed on a mouse embryonic fibroblast feeder layer, they start to grow as undifferentiated colonies. If they are removed from the mouse fibroblasts and placed in different culture conditions, they will begin to differentiate into various developmental stages. To create different types of embryonic stem cells, the growing colonies on the feeder layer are separated using mechanical methods for future use in producing more colonies. This process also involves additional steps, such as proliferation, cryopreservation, and ultimately, the creation of new lines of human stem cells. However, this process is quite labor-intensive, and successfully generating new lines of human

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embryonic stem cells requires a significant amount of expertise [38].

- *Human Studies On Differentiated and Advanced Stem Cells*

The 2004 paper published in the Lancet offered a thorough review of all the research done on this subject. This study emphasized the successful differentiation of stem cells into beta cells, citing earlier studies. In the article, another group showcased the differentiation of human embryonic stem cells into clusters that produce insulin. A team of Korean researchers revealed at the annual Stem Cells conference in July 2004 that they had generated a mass of cells, some of which produced insulin, from human embryonic stem cells. This research suggested that insulin production happened spontaneously, rather than being triggered by glucose [38,48].

- *Stem Cells Sourced from Hematopoietic Organs*

Hematopoietic stem cells found in the bone marrow are unique cells that can replicate themselves over multiple generations and can differentiate into various cell types. Human stem cells have the ability to grow in culture and can develop into all three embryonic germ layers, both in laboratory settings and within living organisms. When these cells migrate to the liver, colon, kidneys, skeletal muscle, heart muscle, and central nervous system, they can transform into specialized parenchymal cells, as observed in both animal studies and in patients who have received bone marrow or organ transplants [48]. In a study focused on direct differentiation, researchers found donor-derived cells in the pancreatic islets of recipient mice several months after bone marrow transplantation. However, only about 1-3% of the islet cells originated from the transplanted bone marrow. Mesenchymal stem cells, which come from adult bone marrow, have a wide range of differentiation abilities. During bone marrow transplantation, isolated-derived cells have been observed to develop into endothelial cells. These endothelial cells send signals to the progenitor cells in the host pancreas, prompting their differentiation. As a result, the blood glucose and insulin levels in diabetic mice returned to normal, and the animals showed improved survival rates [49].

The immune destruction of newly formed beta cells in people with type I diabetes continues to be a major challenge. The non-obese diabetic mouse is often used as a model for studying autoimmune type I diabetes. When bone marrow is transplanted, it can lead to microchimerism, which is when cells from one individual exist within another genetically different individual. If this bone marrow is given before autoimmune diabetes develops, the resulting chimerism might help prevent the disease, likely by interfering with immune regulatory cells and ultimately stopping the host's immune system from attacking the beta cells [47].

Diabetic mice who had bone marrow transplants exhibited normal blood glucose levels after insulin treatment and ultimately achieved recovery. This is likely attributable to heightened proliferative activity of pancreatic tissue and beta-cell regeneration. A research by Kodama shown that the transplanting of spleen mesenchymal cells resulted in the development of beta cells. Under certain settings, spleen mesenchymal transplant cells likely obliterate islet immunity [50].

- *Stem Cells and Their Functions in the Pancreas and Liver*

In isolated pancreatic tissue, pancreatic progenitor cells can differentiate into endocrine islet cells. Recently, scientists have been able to generate islet cells in laboratories from human pancreatic ductal stem cells. The limited developmental potential of islets makes their therapeutic application challenging, as the number of transplanted islets is a critical factor for achieving insulin-free outcomes. In about 25% of patients who underwent transplantation in the Edmonton Islet Transplant Program in Canada, luminal cells are utilized in the protocols. This research indicated that the transplantation of beta islet cells from cadaver donors to diabetic patients led to significant improvements in managing diabetes. Further investigation is needed regarding the likelihood of differentiation and the maturity of cells when implanted into diabetic recipients.

Recent studies have highlighted concerns regarding the ability of pancreatic islet beta cells to independently control and regulate blood sugar levels without assistance from other pancreatic islet cells. Research involving cells from non-pancreatic sources has led to the creation of a diverse cell mass. The functional differentiation of this cell mass in relation to pancreatic islets can only be determined through tests that assess the behavior and function of these cells [51].

The main issue with differentiated cells in culture media is their inability to produce insulin in response to the glucose levels present. While the beta cells in the islets do secrete higher amounts of insulin as glucose concentrations rise, they are not a viable solution. Additionally, under optimal conditions, differentiated cells in the culture medium release a mix of pancreatic hormones. Recent studies from this decade have shown that transplanting pancreatic endocrine progenitor cells, sourced from stem cells, into immunodeficient diabetic rats leads to the differentiation of these cells into islet-like cells that can secrete insulin in response to blood glucose levels, even though they lack all the molecular markers typical of beta cells. However, despite the promising nature of these findings, there are concerns about the risks of transplanting undifferentiated cells, such as the increased chance of teratoma formation and other unforeseen complications, which highlight the need for further research and expertise [38,52].

## IV. CONCLUSION

There is currently no definitive cure for diabetes; however, available medications can slow the progression of the disease and delay the onset of complications. In recent decades, pancreas transplantation has become a common treatment option. Yet, challenges such as a shortage of donors, difficulties in islet purification, risks of disease transmission, transplant rejection, and the declining effectiveness of transplanted β-cells over time continue to be

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significant hurdles. Recently, the application of stem cells in diabetes treatment has gained considerable attention. Stem cells have been utilized in laboratory research and, to some extent, in clinical trials to replace dysfunctional and cancerous cells. To effectively develop suitable treatments involving stem cells, it is essential to gather extensive data and gain a thorough understanding of the properties and behavior of these cells. This knowledge also aids in improving in vitro culture techniques and overcoming biological barriers that hinder their clinical application. Despite numerous studies in this field, more research is needed to clarify how these cells behave within the body and to refine treatment methods for their use in regenerative and personalized medicine. This requires strong collaboration among experts in both fundamental and clinical sciences [47].

While the potential of using stem cells, especially fetal cells, for a definitive diabetes treatment is fascinating, and some animal studies have shown promise, this method has not yet become a standard treatment option after two decades of research. Many challenges and unresolved questions still exist, requiring scientists to develop solutions through various animal and lab studies before applying them to human cases. If successful, this could provide a valuable therapy for those with diabetes. Key challenges in this approach include generating beta cells from stem cells, ensuring these cells function effectively over the long term, preventing teratoma formation, and addressing the ethical concerns surrounding genetic research on stem cells [38].

## V. FUTURE DIRECTIONS

With new technology that potentially changes diabetes therapy, stem cell research has a bright future. A major feat is 3D bioprinting functioning pancreatic tissues or mini-organs. These bioprinted constructs may imitate the pancreas' shape and function by using stem cells and bioengineered scaffolds to provide insulin-producing cells that can easily integrate into the patient's body.

Innovative methods include using stem cell-derived beta cells and artificial pancreas technology. These hybrid systems use real-time glucose monitoring and automated insulin administration to regulate glucose and reduce hypoglycemia and hyperglycemia risks, improving stem cell therapies. Beta cells are being encapsulated in sophisticated biomaterials and injectable hydrogels to prevent immunological rejection and provide appropriate oxygen and nutrition delivery.

Recent advances in single-cell genetics and proteomics may help us comprehend beta-cell growth and malfunction. These findings may boost stem cell-based beta cell production. The use of machine learning and AI to predict patient responses to stem cell therapy, enhance transplantation results, and uncover novel intervention targets is an intriguing new area.

➢ *Abbreviation*

- ADA: American Diabetes Association
- EASD: European Association for the Study of Diabetes
- IPCs: Insulin-producing cells
- ECs: Endocrine cells
- HLA: human leukocytes antigens
- c-myc: cellular Myc

➢ *Author Contributions***:**

The author conceptualized, researched, and drafted the manuscript. They performed a comprehensive review of the literature, synthesized relevant findings, and contributed to the critical analysis of the topic. Additionally, the author revised and finalized the article for publication, ensuring clarity and accuracy.

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➢ *Conflict of Interest*

The authors hereby declare that they have no conflict of interest.

➢ *Consent for publications*

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