

Review Article

The capacity of stem cells in treatment of diabetes



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ABSTRACT

Diabetes, a chronic metabolic disease, is recognized as the most frequent disorder in the endocrine system with hyperglycemia dealing with either insulin resistance or insufficiency or both. This disease is usually associated with numerous acute and chronic complications. Also, the treatment of diabetes complications has imposed a heavy financial burden on most societies. During the last decade, pancreatic islet transplantation has been widely studied as a potential therapy for diabetes. Of course, due to its limitations removing pancreatic cells from the corpse is very difficult. Stem cells are renewable cellular sources that are proposed as a substitute for organ transplantation. These cells which can be found in almost all multicellular organisms are capable of division and transforming into highly specialized cells, they can also replace injured and lost cells. The possibility of using stem cells in diabetes therapy and building insulin-producing islets has long been considered by most scientists and can be a future hope for controlling diabetes. Interestingly, human stem cells derived from hematopoietic organs, liver, pancreas, and embryonic human stem cells are among these factors. In this article, a series of studies carried out on this field is briefly reviewed.

1. Introduction

Diabetes is among the metabolic diseases and as a multi-factorial disorder is characterized by a chronic increase in blood sugar and is caused by either a disorder in secretion or function of insulin or both. Insulin is a hormone that is built in the human body by the pancreas. It takes sugar from the blood and sends it into the body cells so that body can use the sugar as energy. In patients with diabetes, the insulin content is low or due to different reasons, it cannot leave a sufficient effect, so the cells are unable to absorb adequate blood sugar.

Therefore, the sugar or glucose content in the blood increases, and as time passes, it forms damage to several body parts. Diabetes type II is regarded as one of the most frequent non-communicable diseases in the world, and in most countries, it is thought as the main

cause of mortality [1].

Due to its remarkable significance, it can be claimed that diabetes mellitus is the most important cause of blindness in patients ranging from 25 to 75 years old, and is reported as the most significant factor causing limb amputation in the United States. Moreover, 35 percent of patients with chronic kidney failure and dialysis are suffering from diabetes.

This sudden burst of prevalence rate corresponds with the aging of the population along with changes in lifestyles as well as economic development and an increase in the obesity rate. In a study published in 2010, it was shown that diabetes prevalence in the Middle East will experience a significant increase by 2030, and it was also estimated that the annual rate of diabetes in Iran by

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2030 will be ranked second after Pakistan in the region[2]. Here are some of the most common symptoms of diabetes: frequent urination, extreme thirst, extreme hunger (even while eating), exhaustion, blurred vision, slow-healing wound/bruise, weight loss even in case of overeating (diabetes type I), tingling, pain or numbness in the hands or feet (diabetes type II) among adult aging over 40, sleepiness, feeling bored, high blood pressure, and high blood lipids.

Diabetes complications which cover almost all body organs are divided into early and late complications. The only possible way to prevent such devastating epidemics and their subsequent complications is to make significant changes in the lifestyles of the public and to introduce the invoking factors. However, in some people with diabetes type II, the symptoms are so mild to notice. Early diagnosis and treatment of diabetes can lower the risk of infecting with such diabetes-oriented complications[3].

2. Types of Diabetes

The most popular kinds of diabetes are diabetes types I and II. Although the prevalence of these types of diabetes is rising across the world, the frequency rate of diabetes type II is much more than that of type I, mainly due to recent changes in way of living, popular obesity, and reduced physical activities[4]. Diabetes type I is accompanied by a severe reduction in insulin caused by the destruction of pancreatic beta cells that is the result of a phenomenon called self-immunity. In diabetes type II, the amount of insulin secretion is relatively reduced; insulin secretion sometimes even decreases by about 50% [5].

Inadequate secretion of insulin cannot overwhelm resistance to insulin in this disease, so a reduction in insulin secretion is present in both types of diabetes. In fact, in patients who have long experienced diabetes, nearly %99 reported beta cell deficiency cells activity in diabetes type I, whereas, in the case of diabetes type II, this rate ranged from %40 to %60. Controlling diabetes type I requires regular intake of insulin on a daily and frequent basis, but diabetes type II can be controlled by using oral drugs which affect beta cells or the peripheral tissues [6]. There are 5 different groups of second-line antiglycemic

medicines recommended by the ADA and EASD: dipeptidyl peptidase 4 (DPP-4) inhibitors, GLP-1RA inhibitors, SGLT2 inhibitors, sulfonylureas and thiazolidinediones [7].

However, none of these treatments has complete and proper correspondence with the result of the natural biological function of the beta cells. They can neither achieve desirable control nor avoid unwanted side effects [8].

Trying to balance blood sugar regularly can lead to an increase in hypoglycemia in both types of diabetes. In the United States, most under-treatment diabetic patients (type I) had more than %7.5 glycosylated hemoglobin, whereas the average range of glycosylated hemoglobin in Japan among the patients suffering from type I was % 8.2 and for diabetes type II, it was %7.4 (Table 1)[9].

There are also reports on gestational diabetes and other types of diabetes which are related to other diseases. About 3 to 5 percent of pregnant women, especially late in pregnancy, had diabetes. These pregnant women who tended to develop diabetes had numerous risk factors that make them more vulnerable to increased gestational diabetes. Although the disease disappears after childbirth, it may reappear in the next pregnancy. About 50% of women who developed diabetes during pregnancy also developed diabetes permanently. Therefore, it is suggested to inform them about correct preventive programs for both mothers and their children under the supervision of a specialist. Although modern science has proved that diabetes is not a thoroughly-treated complication that is accompanied by diabetes until death, it can be possibly treated by building cooperation between a doctor and a diabetic person to form a very normal situation in which the diabetic person will not create a negative self-image [3].

3. Complications of Diabetes

Diabetes, which causes major side effects in most systems and organs of the body, can result in several early and late complications of the disease that cause disability, paralysis, high treatment costs and even death. Moreover, diabetes has some complications such as cardiovascular complications, nephropathy,

neuropathy, retinopathy and cataracts as well as other problems [10].

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

	Type 1 diabetes	Type 2 diabetes
Occurrence	Incidence of the disease in childhood (under 20 years old)	Incidence of the disease in adulthood (over 40 years old)
Prevalence	Low prevalence (5-10%)	High prevalence (80-85%)
Risk factors	Genetic factors	Genetic factors, lifestyle and environmental factors
	Destruction of beta cells as a result of autoimmunity	Defects in the insulin signaling pathway with impaired insulin secretion
Phenotype	Absolute lack of insulin	Insulin resistance and deficiency
	Exogenous insulin is absolutely essential	Exogenous insulin is required
	Susceptible to ketoacidosis	No ketoacidosis
Genotype	HLA related	No association with HLA
	More than 50% of identical twins are predisposed to T1D	More than 70% of identical twins are susceptible to T2D
Treatment	Insulin injection	Insulin injection, healthy diet and sport

Diabetic ketoacidosis is another complication that frequently occurs mostly in diabetes type I and partly in diabetes type II, especially in disease conditions. It is also caused by an absolute or relative lack of insulin. It has three clinical features: hypoglycemia, ketosis, and acidosis. The complication of hyperosmolar coma syndrome is almost exclusively reported in diabetes type II. The pathogenesis of this disease resembles diabetic ketoacidosis; however, ketosis and acid are not reported in hyperosmolar coma syndrome. In fact, insulin resistance is often present in this disease [2].

Diabetes is the fifth cause of death and the first reason for chronic kidney failure, non-traumatic amputation, and blindness in most countries. According to recent studies, diabetes and its complications (such as cardiovascular and renal eye complications) can be hindered by taking a healthy diet, following regular physical activity, controlling blood sugar, blood pressure, and cholesterol level [12].

Diabetic neuropathy, a common complication of diabetes, is a disorder in the function of the body's peripheral nerves. It is also associated with high mortality and an increase in the economic burden of diabetes

care. In fact, this disorder is a late complication in diabetes type I and an early complication in diabetes type II. The lack of timely diagnosis of diabetes and its complications is a key reason for the relatively high prevalence of this complication. The prevalence of neuropathy in diabetes type I decrease with age, whereas the prevalence of neuropathy increases with age in diabetes type II. Diabetic retinopathy is also an important chronic vision disorder of diabetes that results in low vision and blindness, especially in social and occupational productivity across the world [13].

The presence of thyroid hormones is quite necessary for normal metabolism, so the processes and pathways mediating the metabolism of carbohydrates, proteins and lipids are mostly affected by thyroid hormones in all tissues. Dealing with the accumulation of blood fat and lowering the cholesterol level and increasing the body's metabolism are some possible metabolic effects of thyroid hormones. In diabetic conditions, the output of thyroid hormones undergoes changes, which in turn, result in extensive metabolic and enzymatic changes at the cellular level as well as variation in the normal function of various body cells. Thus, an increase in plasma concentration of

cholesterol, phospholipid and triglycerides is significant in hypothyroidism and their decrease results in hyperthyroidism. Such metabolic changes which are caused by thyroid hyperactivity and hypothyroidism can make up for the deterioration of blood sugar control and result in exacerbation of diabetes. Considering the fact that the main source of the release and thyroid hormones is the follicles of the thyroid gland, changes in the secretion of thyroid hormones can affect the dimension of the follicles and the volume of the thyroid gland [14, 15].

Reducing the effect of insulin on the liver also leads to increased gluconeogenesis and glycogenolysis which are caused by increased hepatic production of glucose. A significant increase in levels of triglycerides and cholesterol in diabetes type I and an increase in triglycerides in diabetes type II prove the occurrence of lipid disorders which are mostly caused by diabetes or possibly by insulin deficiency or resistance against it [16].

In diabetes type I, there is a significant increase in glucose, triglycerides, and cholesterol. Also, there is a decrease in LDL, HDL, and insulin. Many studies have referred to an increase in triglycerides and cholesterol, and a decrease in LDL and hypothyroidism, so it can be inferred that the samples of diabetes type I are probably suffering from hypothyroidism [17]. Moreover, in comparison with the control group, in diabetes type II, a significant increase in the average rate of insulin and glucose and an increase in triglycerides are observed. In this group, changes in LDL and HDL have a slight decrease, but cholesterol remains almost unchanged. In general, diabetes types I and II indirectly affect the structure of the thyroid gland by affecting the body's need for thyroid hormones [18].

Due to decreased activity of lipoprotein lipase, the fat content reduces in the skin of a diabetic person which finally results in a reduced rate of moisture release and dry skin. Lack of collagen which results from a decrease in its production in diabetic skin also leads to more skin vulnerability to external factors. High amounts of glucose in diabetic patients, which also results in dryness and fragility by infection, and eventually leads to wounds, can

prolong wound healing. A diabetic foot ulcer is usually caused by a lack of blood sugar control, peripheral vascular disease, peripheral nephropathy, and immunosuppression [19].

4. Treatment of diabetes

The control of diabetes type I requires the continuous intake of insulin on a daily and frequent basis, whereas diabetes type II can be controlled by oral drugs which leave effects on beta cells of peripheral tissues, yet none of them has a complete and appropriate correspondence with the result of the normal physiological function of beta cells, so they can neither provide the desired control nor leave unwanted side effects [20].

In America, most type 1 diabetic patients who are being treated have glycosylated hemoglobin of more than 7.5%, and the average glycosylated hemoglobin in Japan is 8.2% in type 1 patients and 7.4% in type 2 diabetes patients [21].

It was performed a successful pancreas transplant more than 40 years ago. Since then, several attempts have been made to systematically transfer activated beta cells to patients and re-induce insulin secretion in people with diabetes type I. Pancreas transplantation has been performed only in a small number of patients, especially those who need simultaneously a kidney transplant, mainly due to its possible risks. Moreover, transplantation of islets of Langerhans has received much attention recently. The first successful transplantation was performed in 1999. It was followed by several experiments carried out in transferring these islets to the efferent vein of the liver. Some patients who received islets of Langerhans needed no insulin during the first years, but in long run, the transplanted islets of Langerhans lost their activity and the patients had to re-use insulin. In this way, the main causes for the short life of beta cells were the need for taking immunosuppressive drugs, as associated with the risk of autoimmunity recurrence as well as drug side effects and the limitation in the number of required tissue donors, which in turn, has considerably limited the widespread use of this approach [22].

Recently, applying stem cells in the treatment of diabetes has taken special attention. Studies dating back to about 50 years ago showed that stem cells can divide iteratively and yet, remain undifferentiated. But in presence of a special stimulus for the expression of key genes in the environment, they can make a distinction between different types of specified cells. Thus, great efforts have been done to use stem cells in replacing disabled and malignant cells in laboratory studies and a few have been carried out in a clinical study[23]. Limitations in the number and capacity of reproduction of adult stem cells along with the difficulty of their isolation have led the attention of most scientists to the possibility of using fetal stem cells in the last decade. These cells which have various capacities are able to reproduce themselves frequently. The earliest experimental studies on this issue were issued in 2000. Later, several studies showed that embryonic stem cells can differentiate into insulin-producing clones and in turn, reduce the increased blood sugar in laboratory animals. However, the limiting factor in using beta cells derived from embryonic stem cells is their rejection by the host. This was solved by prescribing immunosuppressive drugs. More recently, the design of capsules has made nutrients exchange possible and penetration of immune cells impossible has contributed to the transfer of these differentiated cells, in this method, embryonic stem cells cultured in vitro are selected for growth-stimulating genetic events such as c-myc replication[24].

5. Stem Cells

Stem cells are defined considering two factors: these cells are capable of self-synthesis, that is, they can perform mitosis divisions to maintain their population and they can also be differentiated into various cells. In the developing embryo, stem cells are able to differentiate into specific types of cells derived from the three main germ layers (ectoderm, endoderm, and mesoderm). The resulting cells can participate in the renewal and replacement of some renewable organs such as blood, skin, and digestive tissues[25]. Adult stem cells are commonly used in medicine. For instance, bone marrow has stem cells that are able to reproduce and differentiate into specific types of cells which

resemble different body tissues (e.g. muscle and nerve). All-powerful stem cells can also produce a living and complete organism even if they have the potential to differentiate into embryonic and extra-embryonic cells. The cells resulting from the first few divisions of the fertilized egg are considered all viable. Pluripotent stem cells, which are actually the children of pluripotent cells, are also able to differentiate into all types of embryonic cells. In other words, they produce all the cells which derive from the embryonic germ layer. Multipotent stem cells differentiate only into the types of cells derived from the germ layer from which they originated, as well as unipotent stem cells which are just able to produce cells that thoroughly resemble themselves [26].

Several factors are involved in regulating the characteristics of stem cells. Besides the role of the microenvironment in terms of its 3-D engineering structure, the interactions between stem cells and the surrounding environment are also quite significant. The characteristics of extracellular matrix components, the presence of specific growth factors and various cytokines, as well as the physical and chemical characteristics of the environment (pH, ion concentration, and presence of metabolites such as ATP), can also control the behavior of stem cells [27].

5. 1. Types of stem cells

In mammals, there are mainly two kinds of stem cells: embryonic stem cells which separate from the inner cell mass of the blastocyst, and mature stem cells which exist among mature tissues and actually act as the body's repair system. The embryonic stem cells extracted from the inner cell mass of the blastocyst are renewable. In a period of 4-5 days after fertilization, the human embryo reaches the blastocyst stage. These cells are so powerful that in presence of specific stimuli, they can differentiate into cells in an adult's body indicating the potential of these cells in creating teratoma (is a rare type of germ cell tumor that may contain immature or fully formed tissue, including teeth, hair, bone and muscle). Noteworthy, these cells cannot differentiate into extra-embryonic cells. Embryonic stem cells express transcription factors and specific cell surface proteins.

Inhibiting differentiated genes has made these factors the main controller of embryonic stem cell pluripotency [27]. There are numerous challenges to using human embryonic stem cells since extraction of these cells requires the destruction of blastocytes, yet, according to some moral and religious schools of thought, it is not reasonable. To solve this problem, it was suggested to use other types of stem cells such as adult stem cells, amniotic stem cells and induced pluripotent stem cells [27].

5. 1. 1. Embryonic stem cells

Embryonic stem cells are primitive stem cells that are placed in different organs of the fetus. There are two types of embryonic stem cells.

Fetal-specific stem cells, which are obtained from the tissues of aborted fetuses, are not immortal, but have a high dividing power and are multipotent.

Extraembryonic stem cells, which are derived from extraembryonic membranes, cannot be distinguished from adult stem cells. In fact, they are accessible after birth and have a high potential for cell division and pluripotency. Multipotent stem cells are also available in amniotic fluid. Despite their high activity, they are incapable of tumorigenesis but can differentiate into fat, bone, muscle, liver, and nerve cells [28].

Umbilical cord blood stem cells: mesenchymal cells which stem from the umbilical cord are multipotent, yet they lack the markers of blood cell arrays. Two other significant features of these cells are their low immunogenicity, mostly defined by low expression of MHC antigens and lack of stimulation in the proliferation of allergenic lymphocytes. Mesenchymal cells have the capacity to differentiate into mesenchymal tissues such as bone marrow, cartilage, muscle, tendon and fat [29].

5. 1. 2. Mature stem cells

Adult stem cells, also known as body stem cells, are specifically involved in maintaining and repairing tissues. They exist in both children and adults. Adult pluripotent stem cells which are rare can be found in small

numbers in umbilical cord blood and some other similar tissues. However, bone marrow is a rich source of adult stem cells which are frequently used in different researches. The fact is that the number of mature bone marrow stem cells decreases with age, and interestingly, it is higher in men than in women during reproductive years. Most adult stem cells are multipotent, so they are usually named after their original tissue. Of course, achieving them does not depend on using the embryos and does not have the mentioned ethical restrictions. Moreover, since these cells are used as autographs, they do not make the risk of tissue rejection [27].

Bone marrow stem cells: Bone marrow is the main source of adult stem cells. There are two main types of stem cells in the bone marrow: (1) bone marrow stem cells which are actually the first progenitors of blood cells and tend toward all types of blood cells, both myeloid and lymphoid.

Bone marrow stromal stem cells: In fact, they are non-hematopoietic cells that can be found in the bone marrow and are called mesenchymal stem cells. Mesenchymal stem cells are multipotent stem cells that can differentiate into various types of cells in both laboratory environments and body environments [30]. In addition to bone marrow, there are other sources known as tissue-specific mesenchymal stem cells which are used for obtaining mesenchymal stem cells. Some are mesenchymal stem cells taken from adipose tissue, skeletal muscle, and milk teeth.

Mature stem cells obtained from fat: these cells are usually isolated from fat tissue through liposuction. Seemingly, this population of cells is greatly similar to mesenchymal stem cells obtained from bone marrow. In the laboratory, they are able to differentiate into bone, cartilage, fat, muscle, and possibly nerve [31].

Neural stem cells: the limited presence of these cells is somehow approved in the regions of the lateral ventricles of the brain and the dentate gyrus [32].

Mature olfactory stem cells: these stem cells are isolated from human olfactory

mucosa cells. It is possible to change the nature and power of cells via special stimulating or inducing factors, and in turn, produce cells with high differentiation ability [33].

Induced pluripotent stem cells: these are a kind of pluripotent stem cells that are produced directly from adult stem cells. Here, the patient does not experience the problem of incompatibility, since the challenge of using embryos is solved. Multipotent cells have numerous applications in regenerative medicine mainly due to their indefinite multiplication. They can also easily turn into any other type of cell in the body such as neurons, heart cells, pancreatic cells, and liver cells which as a unique source are able to prevent diseased or damaged cells.

In many ways, induced pluripotent stem cells resemble natural pluripotent stem cells among which are a similar way of expression of specific genes and proteins in stem cells, chromatin methylation pattern, doubling time, formation of embryonic bodies, teratoma formation and living chimera formation [34].

Also, these cells have several limitations. Some reprogramming factors are carcinogenic, and genomic incorporation of transcription factors can be associated with the risk of inducing mutations to the genome of target cells.

As shown in some studies, due to their ability to make cells with the origin of all three embryonic germ layers using stem cells, these cells can be applied in the synthesis of tissues and organs [35].

6. Stem cell transplantation in the treatment of diabetes

Fortunately, induced multipotent cells have provoked unprecedented hope in tissue replacement. However, they have not been able to meet the needs for replacing beta cells and treating diabetes. In fact, creating active beta cells from new or induced stem cells requires their successful differentiation as well as passing the developmental stages normal beta cells have gone through. Also, inducing this differentiation needs precise identification of transcription factors and

small molecules which affect the expression of these factors or metabolic enzymes or surface transporters. In this process, some genes should be inactivated and others should be induced. In other cases, it is even required to substitute them with other versions which are carried by several foreign vectors such as viruses [36].

The first study that analyzed the therapeutic effects of stem cells in the treatment of patients with type 1 diabetes is related in 2003 in Brazil, since then other centers in different countries have started their clinical trials [37]. Some of the studies that investigated the effects of stem cells, challenges and advances in the treatment of diabetes are listed in Table 2.

6. 1. Experiments on embryonic stem cells of animal origin

The Rat embryonic stem cells grow undifferentiated when exposed to leukemia inhibitory factors. After providing suitable conditions for the differentiation of different cell lines by directing them towards pre-selected pathways to specific cell lines, they are differentiated and evolved.

Regarding remarkable homogeneity between the evolutionary paths of the pancreas and the central nervous system, a large number of researches have initially attempted to direct embryonic stem cells to nerve cells, and then by performing genetic work and interventions such as changing the culture environment by adding growth factors, they sought to achieve pancreatic islet beta cells [38].

Among great studies carried out on rats 'embryonic stem cells and their transformation into insulin-producing cells is the experiment by previous research [39]. Which has been cited frequently by various groups? In this study, based on similarities between the developmental control mechanism of the central nervous system and the pancreas, some neuron production methods have been used to transform embryonic stem cells into pancreatic cells [39].

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

The title of the study	Study type	Overall result	Writers
Stem cell therapy for diabetes: do we need to make beta cells?	Descriptive research-analytical	Type 1 diabetes can definitely be cured with the help of stem cell transplantation. Stem cells are a potential source for the generation of large numbers of insulin-producing cells as long as their functional phenotype is that of pancreatic beta cells.	[40]
The Potential for Stem Cell Therapy in Diabetes	Descriptive research-analytical	The major achievements in the isolation, culture and differentiation of EC cells compared to the pancreas transplantation method create the hope that it is possible to use beta cells in the treatment of diabetes.	[41]
Stem Cell Therapies in Regenerative Medicine and Diabetes Mellitus: Advances, Constraints and Future Prospects	Descriptive research-analytical	This study examines the types of stem cells, their production sources and their effectiveness in the treatment of both types of diabetes. It also expresses moral and religious concerns in some countries due to the use of embryonic stem cells.	[37]
Stem Cell Technology for the Treatment of Diabetes	Descriptive research-analytical	Among all embryonic stem cells, pancreatic cells are the most well-known stem cells with high efficiency and excellent capacity for reproduction. After differentiating into insulin-producing cells and forming island-like structures in laboratory conditions, these cells are able to secrete insulin and help reduce hyperglycemia.	[42]
Stem Cell Therapy in Diabetes	Descriptive research-analytical	Mesenchymal stem cells (MSCs) are multipotent stem cells that have the ability to transform into beta cells and secrete insulin.	[43]
Stem cell therapy for diabetic foot ulcers: a review of preclinical and clinical research	Analytical research	Stem cells of adipose tissue in response to injuries and wounds on the legs of diabetic patients migrate to the vessels of the injury site. Then, by creating angiogenesis, preventing tissue fibrosis and increasing oxygen supply to the injury site, they save the damaged tissue.	[44]
Stem Cell Therapy: Recent Success and Continuing Progress in Treating Diabetes	Descriptive research-analytical	The results of this study consider the access to stem cells as the definitive method of treating diabetes, but the expensive costs for the preparation, maintenance and maturation of stem cells are among the major problems of this method[45].	[45]
Current progress in stem cell therapy for type 1 diabetes mellitus	Analytical research	Stem cell-based therapy is proposed as a promising potential treatment method for the treatment of diabetes, especially type 1 diabetes. The main focus in the present study is the differentiation of IPCs from hPSCs, which are more efficient in the secretion of glucose-responsive insulin in patients with type 1 diabetes.	[46]

Monkey embryonic stem cells have further been transformed into insulin-producing cells by spontaneous cell differentiation. In this way, the growth factor, beta-oxendin-4, was

used for cell differentiation and development. Moreover, to confirm insulin production by the cells produced from embryonic stem cells, C-peptide measurement was evaluated[47].

6. 2. Experiments on embryonic stem cells of human origin

Human embryonic stem cells can transform into insulin-producing cells under appropriate conditions in a culture medium. A major distinction between embryonic stem cells in humans and mice is that the leukemia limiting factor causes the undifferentiated proliferation of embryonic stem cells in the latter, yet it has no significant effect on human embryonic stem cells. For undifferentiated proliferation, it is required to put human embryonic stem cells on a feeder cell layer. After the human embryonic stem cells are placed on the mouse embryonic fibroblast as a feeder layer, they start growing as undifferentiated colonies. If they separate from the mouse embryonic fibroblast and be placed in other cultural environments, they will differentiate into various levels of training. Also, to produce different types of embryonic stem cells, the growing colonies on the cell feeder layer are separated using mechanical methods to be later used in producing other colonies. This stage is accompanied by performing other processes such as proliferation, freezing, and ultimately, producing new lines of human stem cells. However, this process is time-consuming and success in the production of new lines of human embryonic stem cells requires a great deal of relevant experience [38].

6. 3. Human studies conducted on evolved stem cells

The 2004 article in *Lancet* magazine was a review of all the work done on this subject. While referring to past studies, this study emphasized the successful differentiation of stem cells into beta cells. In the journal, stem cells; another group introduced the differentiation of human embryonic stem cells into insulin-producing clusters. A group of Korean researchers at the annual conference of Stem cells hold in July 2004 announced the production of cell mass, in which some cells contained insulin, from human embryonic stem cells. In this report, it was stated that insulin production was spontaneous, but it was not in response to glucose [38, 48].

6. 4. Stem cells derived from hematopoietic organs

Bone marrow hematopoietic stem cells are clonogenic cells that can offer multi-generation renewal and differentiation. Human stem cells are also able to proliferate in culture and differentiate into all three embryonic germ layers in the laboratory and living culture. After entering the liver, intestine, kidney, skeletal muscle, heart muscle, and central nervous system, these cells change into parenchymal cells are present both in animal models and in human bone marrow or organ transplant recipients [48].

In a direct differentiation study, donor-derived cells were found in the pancreatic islets of recipient mice about months after bone marrow transplantation. However, only % 1-3% of the islet cells originated from the transplanted bone marrow. It was represented mesenchymal stem cells' multiple differentiation properties deriving from adult bone marrow. In bone marrow transplantation, the differentiations of isolate-derived cells into endothelial cells were reported. These endothelial cells send signals to the progenitor cells of the host pancreas to stimulate their differentiation. Thus, the reported blood sugar and insulin levels of diabetic mice were normal and the mice had higher survival rates [49].

Moreover, immunological destruction of newly produced beta cells in patients with diabetes type I is still a serious concern. The non-obese diabetic mouse is an animal model of autoimmune diabetes type I. Bone marrow transplantation induces microchimerism (the presence of cells from one individual in another genetically distinct individual), so if the bone marrow is injected before the development of autoimmune diabetes, chimerism will prevent diabetes, probably involving the interference mechanisms of immune regulatory cells, and finally results in prevention of the host cell from the immune response to beta cells [47].

Bone marrow transplanted diabetic rats found normal blood sugar levels when they were treated with insulin and were finally recovered. It is probably due to increased proliferative activity of pancreatic tissue and beta cell regeneration. In another study

conducted by Kodama, transplantation of spleen mesenchymal cells led to differentiation of beta cells. Under certain conditions, spleen mesenchymal transplant cells probably destroy islet immunity [50].

6. 5. Stem cells in pancreas and liver

In isolated pancreatic tissue, pancreatic progenitor cells can turn into endocrine islet cells. More recently, islet cells were produced in laboratories from human pancreatic ductal stem cells. The limited development capacity of islets makes their clinical use difficult since the mass of the transplanted islets is a key factor in determining achieving the stage of insulin-free injections. In about 25% of transplanted cases in the Edmonton Islands in Canada, islet transplantation protocol are luminal cells. In this study, the allocation of beta islet cells from the cadaver and its transplantation to diabetic patients led to significant improvement in diabetes. Yet, further investigation is required in terms of differentiation probability and cell adulthood when implanting to the diabetic donor.

However, more recent findings have posed questions on the capability of pancreatic islet beta cells in controlling and regulating blood sugar independently and in absence of other pancreatic islet cells. Studies and activities carried out on cells with origins other than the pancreas have led to the formation of a cell mass which consists of different cells. Functionally, the differentiation of this cell mass with pancreatic islets can only be recognized via using tests related to the behavior and function of these cells[51].

The most significant shortcoming of differentiated cells in the culture medium is their inability to produce insulin in proportion to the glucose concentration in the medium. Although the beta cells in the islets secrete increased insulin content in proportion to the increase in glucose level, these cells cannot provide such a solution. Also, differentiated cells in the culture medium secrete a mixture of pancreatic hormones in the most optimal case. Some studies in this decade have shown that the transplantation of progenitor cells of pancreatic endocrine cells derived from stem cells to diabetic rats with immunodeficiency leads to the differentiation of these cells into

cells that are similar to islets that were able to secrete insulin according to the blood glucose level, even though they lack all the molecular cell indicators of beta cells. Moreover, although these experiences were promising, due to the concern about the risks of transplanting undifferentiated cells, which increases the chance of teratoma formation and unforeseen complications, they still need further studies and experience [38, 52].

7. Conclusion

There is no definitive cure for diabetes, but currently available treatments can stop the progression of the disease and delay the onset of complications. Pancreas transplantation has been one of the most common treatment methods in the past few decades. However, due to the lack of donors, limitations in islet purification, the risk of disease transmission, transplant rejection, and the re-inefficiency of the received β -cells over time, it has always been a challenge. In recent years, the use of stem cells in the treatment of diabetes has received special attention. The attempt to use stem cells in order to replace the disabled and malignant cells has been used in laboratory studies, and also in small numbers in clinical studies. Generally, achieving a suitable therapy for stem cells requires gathering sufficient knowledge and a thorough understanding of the nature and behavior of these cells. It also leads to the promotion of in vitro culture methods and the removal of biological obstacles which are related to their clinical application. Despite frequent researches done in this direction, more studies are still needed to determine the behavior of these cells inside the body and to idealize treatment methods on their use in restorative medicine and individual medicine. This requires close cooperation between basic and clinical science experts[47].

Although the theory of using stem cells, and especially fetal cells, is really interesting for definitive treatment of diabetes and providing an ideal treatment and of course, some animal experiments are promising, after two decades since the advent of this research, as mentioned earlier, its use as a common method is not possible for treating diabetes. There are still plenty of problems and unresolved questions, which require scientists

to find solutions for numerous animal and laboratory experiments to re-enter human experiences. If successful, it can be used as a useful treatment for diabetic patients. Creating beta cells differentiated from stem cells, ensuring the long-term stability of activities of the formed cells, not creating teratomas, and answering numerous ethical issues that arise in genetic research on stem cells are some of the important issues that are still present in this method [38].

To sum up, although the treatment of diabetes by cell replacement method requires acquiring new skills to overcome the cellular regulatory systems in humans, some scientists believe that this goal is not farfetched. It seems probable to witness its realization in near future.

Abbreviation

ADA: American Diabetes Association
 EASD: European Association for the Study of Diabetes
 IPCs: Insulin-producing cells
 ECs: Endocrine cells
 HLA: human leukocyte antigens
 hPSCs: Human pluripotent stem cells
 MSCs: Mesenchymal stem cells
 T1D: Type 1 diabetes
 T2D: Type 2 diabetes

Conflict of Interest

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

Author's contributions

All authors had equal role in study design, work, statistical analysis and manuscript writing.

Consent for publications

All authors have read and approved the final manuscript for publication.

Availability of data and material

The authors have embedded all data in the manuscript.

Ethics approval and consent to participate

The authors did not use human or animals in the research

Reference

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