

The Application of Stem Cell Therapy on Type 1 Diabetes

Xueqian Huang^{1, †}, Gezhi Ma^{1, *, †}

High school department, Beijing Huijia Private School, Beijing, China

*Corresponding author: 24magezhi@huijia.edu.cn

†These authors contribute equally.

Abstract. Type 1 diabetes (T1D) is also known as insulin-dependent diabetes caused by autoimmune reactions in the patient's body. T1D is caused by the destruction of the pancreatic β cells of the patient by their immune system in the case of autoimmunity. It can lead to dehydration, frequent urination, potential damage to many organs in the body etc. If left untreated, it can lead to death. Consequently, research groups have invested a huge effort to develop possible treatments for. Currently, the existing solutions for T1D mainly include insulin therapy and immunotherapy, but the high costs of insulin therapy and the adverse reactions associated with immunotherapy limits the efficacy of these treatments and are therefore imperfect. To this day, there is no permanent cure for T1D, many study groups have proved that stem cell therapy could provide a possible solution because of its success in curing other diseases. Stem cell therapy is a treatment in which pluripotent or multipotent cells are transplanted into a patient's body in a certain way to restore normal function. The capacity to differentiate into different cell types can help stem cells stop the process of β cell destruction, preserve remaining beta cell blocks, and promote the regeneration of primary beta cells. This review provided an overview of the existing therapies available to treat T1D, gathered information from previous clinical trials and emphasized the importance of stem cell therapies based on the current state of art.

Keywords: T1D; stem cell therapy; insulin; immunotherapy.

1. Introduction

Type 1 diabetes (T1D) is a common type of autoimmune disease affecting 9 million people worldwide). It is characterized by the disability of an individual to produce insulin due to autoimmunity [1]. The immune systems of T1D patients erroneously target the patients' pancreatic β cells, as foreign antigens and conduct immune responses targeting these β cells. This process damages the patients' ability to produce insulin and lowers their blood sugar levels, leading to hyperglycemia. Some of the major symptoms of T1D include polyuria, polydipsia, weight loss, and ketoacidosis [1]. In the long run, T1D negatively affects the patient's cognitive functions, the retina, and the heart. Consequently, the lives of diabetic patients are under significant threat from T1D if not treated. Although the exact cause of T1D is yet to be revealed, data has shown that it is associated with family ancestry and peaks in teenage children [1].

Traditionally, the most widely used therapy to combat T1D is insulin injection. Insulin enables the patient to lower blood glucose levels to avoid hyperglycemia and all its consequences. As a result, insulin therapy has significantly elongated the lives of T1D patients over the last decades. However, T1D patients are dependent and do not fully recover with the help of insulin and depend on insulin injections throughout their lives. Injections lead to dramatic fluctuations in the insulin levels in the patient's bloodstream, and the doses are not affected by the per-meal glucose intake, leading to hypoglycemia. Hypoglycemia and many other complications of insulin therapy reduced 11.1 and 12.9 years of life expectancy, respectively, for male and female patients. Financially, the life-long dependence of T1D patients on insulin and the high costs of the drug means a high expenditure for governments and individuals [2, 3]. The transplantation of entire livers can solve the problem of insulin level fluctuation and glucose unresponsiveness. Another therapy, immunotherapy, is recently used on T1D patients. This approach aims to block the immune pathways of T cells towards

pancreatic β cells. Despite the associated complications, immunotherapy was ineffective against the disease in the late stage of T1D when autoimmune attacks already kill most β cells.

To solve this issue, scientists have constantly been working on stem cell therapy to restore insulin-secreting cells into the patients' bodies. Stem cell therapy transplants human embryonic stem cells (hESCs), induced pluripotent stem cells (iPSCs), or mesenchymal stem cells (MSCs) and signals them to mature into insulin-secreting cells after being transplanted into patient's bodies. These cells are designed to secrete insulin in accordance with fluctuation blood glucose levels to control the blood sugar level effectively. Furthermore, cases of pancreas transplants have ended the insulin dependence of some patients, demonstrating the promise of the transplantation of cells that can produce insulin as a cure for T1D. Nonetheless, the patient's immune system will constantly attack the re-established insulin-secreting cells in the patient's body after the transplantation. Immune system modulations such as immunotherapy are needed to maintain the transplanted cells.

This review briefly summarized the existing therapies and stem cell therapy for T1D. Then, it made comparisons and talked about the advantages and challenges of the latter. Lastly, the review discussed the possibilities of stem cell therapy in treating T1D in the future.

2. Existing therapies of T1D

2.1. Insulin therapy, the traditional drug for T1D

Insulin is a hormone secreted by β cells of the pancreas, in accordance with blood glucose levels. It consists of an A chain and a B chain, connected by a disulfide bond [4]. Naturally, pancreatic β cells release pro-insulin, which then matures breaking into insulin and c-peptide. Insulin injection resolves the complications of T1D by manually supplanting the lacking hormone. Insulin injection therapy uses manually synthesized insulin to replace the insulin, which ought to be produced by the patient's pancreas.

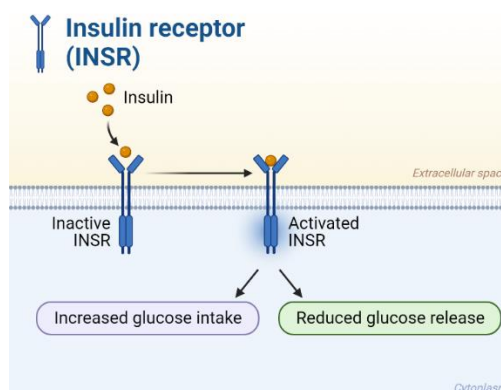


Fig. 1 The mechanism of insulin [5].

Insulin is the only hormone that lowers blood sugar, can treat T1D, and reduce the risk of associated complications [6]. The hormone targets insulin receptors (INSR) to trigger metabolic signals that promote the intake and reduce the release of glucose in fat, muscle, and liver cells as shown in Fig.1 [5]. However, pancreatic β cells release insulin in accordance with blood glucose levels continuously throughout the day. The amount released at each time period during the day varies by person and food intake. Therefore, it is practically impossible to fully mimic this pattern by manual injections. Overall, insulin injection can significantly elongate the lives of T1D patients but fails to cure the disease.

2.2. Immunotherapy, a rising star for T1D treatment

Immunotherapy aims to restore balance in the patient's immune system and delay the occurrence of autoimmunity. Autoimmunity occurs when the immune system of individual launches an immune response to a self-antigen, damaging their cells and tissues and possibly causing diseases. In the case

of T1D, one or more islet-specific antigens are targeted by CD4⁺ and CD8⁺ T cells which activate and become autoreactive intolerant T effector cells (Teffs) [6]. The Teffs break the balance between Teffs and T regulatory cells (Tregs), and then migrate to the pancreatic islets and kill large quantities of pancreatic β cells.

Scientists have invested considerable effort to re-establish the tolerance of Teffs against islet-specific antigens by inducing Tregs or administering anti-CD3. Anti-CD3 is a class of proteins that reduce the activity of Teffs, including OKT3 and teplizumab as shown in fig.2. Anti-CD3 plays a positive role by enhancing the regulation of the immune system, slowing down the breakdown of the balance between Teffs and Tregs, and helping restore pancreatic β cells and delay the occurrence of T1D.

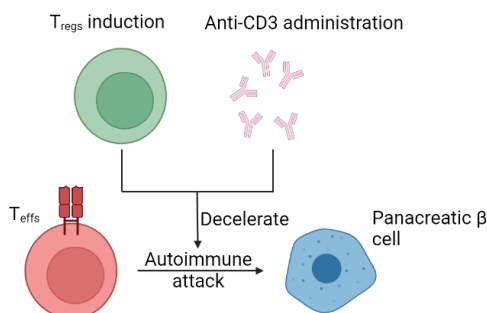


Fig. 2 The mechanism of immunotherapy against T1D [6].

3. Stem cell therapy, a prominent permanent solution to T1D

Stem cell therapy focuses on re-establishing glucose-responsive insulin-secreting cells in the patient's body from hESCs, iPSCs, or MSCs. These three types of cells can potentially become any cell type under preferred conditions. Research advancements to different degrees have been made on all three cell types.

hESCs are derived from human embryos. In this case, stem cells are extracted from the pancreatic tissues of embryos between the ages of 6-14 weeks. Over the past decades, scientists have tried to understand the formation process of endoderm cells, aiming to induce hESCs to mature into insulin-secreting cells by signaling. In 2007, a group of researchers managed to create cells that secrete insulin in response to blood sugar with the help of a critical growth factor, activin A [7]. Another study in 2014 successfully reversed diabetes using insulin-secreting, hESC-derived β cells in mice several months after transplantation [8].

iPSCs are extracted from adult somatic cells and reverted to pluripotent stem cells. A research team, in 2015, published a suspension protocol for differentiating human iPSCs in both vivo and vitro (mice) [9]. A study in 2020 reported an improved protocol generating insulin-producing cells that have shown equivalent efficacy as human β cells in mice, more potent than the ones generated by previous protocols [10].

MSCs are cells extracted from adult tissue that have not fully developed. A study in 2022 showed that MSCs decreased overt diabetes in NOD mice and significantly increased their blood glucose levels [11]. MSCs can be directly donated and transplanted; or turned into iPSCs, modified, and transplanted afterwards. Therefore, the cell type has undergone the most clinical trials.

4. Clinical trials of stem cell therapy in T1D

Since stem cells were first discovered decades ago, efforts and trials have been continuously made to bring stem cell therapy for T1D to reality. In the past fifteen years, clinical trials have been done in many parts of the world, testing the efficacy and reliability of stem cells.

A study in 2007 used a type of MSC treatment: autologous nonmyeloablative hematopoietic stem cell transplantation (anHSCT) among a group of 23 T1D patients (age 13-31 years). After 7-58

months (mean, 128 weeks) of follow-up, twelve patients maintained insulin independence for 14-52 months (mean, 31 months). Moreover, the participants from the aHSCT group reduced their HbA1c levels to 7.0% and their C-peptide levels increased from 225.0 g/L to 728.1 g/L 24 months after transplantation [12].

A clinical trial conducted in 2012 with 65 participants used hematopoietic stem cells, a type of MSCs. According to the research, the β cell function of all 65 participants improved after the transplantation. 59% of participants remained insulin independence for more than 6 months. and median participant of 12 months of insulin independence with decreased dosage demands of insulin afterwards [13].

In 2017, another study group reported a clinical trial in 12 newly diagnosed T1D patients (age 12-35 years) using another type of MSC treatment: autologous hematopoietic stem cell transplantation (aHSCT). With similar initial baselines, the aHSCT group showed notably higher levels of fasting C-peptide as compared to the insulin-only group. Moreover, both the numbers of CD3+ and CD4+ T cells in the patients' body and the α to β cell ratio were significantly reduced [14].

In summary, the three clinical trials conducted over 5-year spans have shown improving results from stem cell therapies from glucose levels to temporary insulin independence and finally α to β cell ratio. Although permanently successful cases are yet to be done, the existing clinical trials have already demonstrated considerable potential for the development of stem cell therapy into a long-term treatment for T1D.

5. Strengths of stem cell therapy in T1D

5.1. Appropriate long-term treatment for T1D

Stem cell therapy promotes blood vessel regeneration and allows cells to grow in place by secreting cell growth factors, which can restore normal islet function. Pluripotent stem cells have a robust self-renewal and differentiation ability. As they are induced to differentiate into β cells, insulin levels in the patient's body is increased and maintained. Thus, this helps diabetic patients to wean off insulin medication. Stem cells injected into the body can live for a long time, and while they are alive, they repair damage and monitor health. Therefore, compared with other treatment options, stem cell therapy fundamentally treats T1D and is the long-term treatment option for T1D.

5.2. Avoid people from having adverse reactions

Stem cells are primitive, undifferentiated cells that have very low immunogenicity, so they can avoid rejection of stem cell therapy in diabetic patients. The cellular preparations used in stem cell therapies are made in a laboratory, where conditions are ensured that they will not be contaminated in the process. And cellular preparations go through multiple safety tests to make sure they don't contain any harmful substances, including bacteria, viruses, endotoxins, and heavy metals. This prevents people from developing adverse reactions such as allergies and inflammation.

5.3. An adequate source of cell donors

Stem cell therapy involves transplanting healthy stem cells into a patient to treat disease. Due to this nature, there is a large variety of cell types that donors can provide. Common cell types that donors can provide include hESCs, MSCs, iPSCs and more [6]. Patients with diabetes can choose to use autologous stem cells or allogenic stem cells. Autologous stem cell, which are their own stem cells, are extracted from the patient's blood tissues, adipose tissues, and bone marrow tissues. These cells are relatively more effective at avoiding inflammatory reactions. On the contrary, allogenic stem cells, are extracted from tissues of other stem cell donors. The use of allogeneic stem cells requires making sure that there are the transplanted allogenic stem cells would not cause inflammatory reactions in the patient's body. For the extraction of both types of cell origins, umbilical cord blood is usually used because its surface antigenicity is weak enough, and therefore, is hard for the recipient's immune system to recognize [15].

6. Organization of the Text

6.1. Safety of stem cell therapy for T1D

About 50,000 clinical treatment cases have been conducted on stem cell therapy. Most of which have reported no adverse reactions such as rejection or allergies, indicating that stem cell therapy is largely safe for use [16]. However, there is little experience with using stem cells as a treatment to T1D. To this point, there are only about 170 such clinical trials according to the Clinical Trials Network in the United States [17]. Although a fraction of these patients achieved insulin independence for several months after transplantation without adverse effects. However, some patients were reported with inflammatory effects, nausea, vomiting and more. The number of clinical trials for stem cell treatment for T1D and the number of patients involved in these trials currently is fairly limited. Therefore, safety cannot be guaranteed for the stem cell therapy for T1D.

6.2. Reliability of stem cell therapy for T1D

Stem cell therapy involves a complex process including the extraction, cultivation, storage, and differentiation. To ensure that stem cells can be produced successfully, these steps need to be carried out under strict experimental conditions. In addition, different amounts of stem cells need to be injected depends on the severity of the disease. The more severe the disease, the more stem cells are needed. Therefore, the strict preparation conditions and the considerable quantity of stem cells required by the T1D patients may significantly increase the cost of the stem cell therapy as a cure for the disease. Generally, a single injection costs between \$5,000 and \$50,000 [18]. Therefore, the high costs associated with stem cell therapy as a treatment for T1D daunts many T1D patients.

6.3. Effectiveness of stem cell therapy for T1D

Stem cell therapy transplants stem cells and induces them to become insulin-secreting cells inside the patient's body. Theoretically speaking, stem cell therapy is a viable and effective solution to T1D. However, current studies on stem cell treatments for T1D are all primary, so the effects of the treatment are not clear-cut, and more clinical trials are needed to prove its effectiveness.

7. Conclusion

The incidence of T1D is mainly based on a certain genetic background, and there are also environmental factors including viral infection. T1D affects people around the world, but as an autoimmune disease, it is difficult to completely cure, so there is no perfect treatment for T1D. Stem cell therapy is a relatively cutting-edge treatment for T1D, and it has many advantages over insulin and immunotherapy. It not only solves the problem that insulin can only be treated for a short period of time and requires continuous injection, but also avoids the serious adverse reactions that can occur with immunotherapy. The mechanism of stem cell therapy matches the cause of T1D, so scientists have been looking for ways to use stem cell therapy to restore beta cells to the patient's body so that it can produce sufficient insulin. The advantages of stem cell therapy are significant. It could be a long-term treatment for T1D, avoid adverse reactions, and have a sufficient source of cell donors. At the same time, using stem cell therapy to treat T1D has some limitations. With few clinical trials, the safety, reliability, and effectiveness of stem cell therapies cannot be assured. Stem cell therapy is a prominent research direction for the treatment of diabetes. However, it is far from maturation because this treatment has not been widely used in clinical diabetes treatment. It will take a long time for stem cells to be used as a treatment for T1D, as more clinical trials are needed for more mature research results. Based on existing research and clinical trials, stem cell therapy has been shown to be moderately effective and can maintain insulin independence for a long time, but relapse is still possible. Considering many factors, stem cell therapy is expected to be the best treatment for T1D in the future.

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