An Overview of Recent Advances in Type 1 Diabetes Therapies

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Abstract. Type 1 diabetes(T1D) is an autoimmune disorder caused by the destruction of pancreatic beta-cell, with both genetic and environmental triggering factors. Many patients need to rely on injecting insulin to replace human insulin and survive, but it is hard to avoid other complications, as there are no complete methods to cure T1D yet. Many therapies other than insulin therapy are developing in progress with many unsolved problems. For example, challenges like safety problems, low production efficiency and feasibility are still overcoming. In this review, factors contributed to T1D and main types of T1D therapies with their recent advances are summarized, including advantages and current problems of therapies. This review can provide a general view of therapies for researchers interested in T1D. In the future, research is still needed, focusing on solving immune challenges in the long run and how to produce beta cell function normally by human body to completely cure the disease.

Keywords: Type 1 diabetes, insulin, immunotherapy, stem cell, beta-cell replacement.

1. Introduction

Type 1 diabetes (T1D) is an autoimmune disorder characterized by destruction of pancreatic beta cells, resulting in insulin deficiency and hyperglycemia [1]. Hyperglycemia is a condition that occurs when blood glucose concentration rises above the normal range. Without insulin, severe diabetic ketoacidosis will occur [1]. Type 2 diabetes is caused by non-autoimmune progressive loss of insulin secretion [2], which is different from T1D.

Factors contributing to T1D are uncertain. Some researchers suggest a potential relationship between low-grade enteroviral infection and islets, others suggest that bacteria play a crucial role in development of T1D [3]. So, T1D patients need persistent insulin therapy to reach their basic insulin needs.

Both prevalence and mortality rates of T1D increase over time. In 2021, there were about 8.4 million people around the world having T1D, and 18% of patients are under 20 years old [4]. About 0.5 million new cases are diagnosed and about 35000 non-diagnosed individuals die within 12 months of symptomatic onset [4]. While there is an increasing population having T1D, great burden given to patients remains. Patients need to pay for high treatment costs and face challenges such as decreased life expectancy and long-term complications [1].

Traditional therapies, like insulin injection and insulin pump are used regularly, whereas novel treatments including immunotherapy and beta cell replacement therapy are popular in recent years. All of them have benefits and limitations. Insulin injection is typical, but it requires multiple daily injections if used and can easily cause fluctuation in blood glucose concentration. Beta cell replacement therapy includes pancreas transplantation and islet transplantation. It aims to maintain normoglycemia by inhibiting endogenous and regulated secretion of insulin and other hormone from the pancreas [5]. Beta cell replacement therapy can immediately stop using insulin therapy, avoid hyperglycemia and improve quality of life, but the limited donor supply and lifelong demand for immunosuppressant therapy are still challenges [1]. Recently, T1D still cannot be cured as most of the treatment can only manage the disease, and new therapies, such as beta cell replacement and immunotherapy, are developing in process. But through research development of novel treatments like stem cell therapy, T1D may be a curable disease in the future.

This article aims to summarize the result of a recent study on main treatments in T1D, reviewing their effectiveness and challenges.

2. Factors Contributed to T1D

T1D is caused by the loss of beta-cells in the pancreas by the adaptive immune system [6]. Factors that promote this process are divided into genetic factors and environmental factors [6]. They result in autoimmune attacks by recognizing beta-cells as autoantigens [6]. The more autoantigens a person has, the greater risk of T1D he bears [6].

2.1. Genetic Factors

T1D is a multifactorial disease [6]. Several genes, including those influencing the human leukocyte antigen (HLA) loci, are among these influences [6]. HLA region is an important part in immune system that focus on antigen presentation, which also include HLA loci. The mutations in the HLA region of chromosome 6p21 are a major susceptibility locus that has been shown [6].

2.2. Environmental Factors

Environmental factors include diets, viruses, seasonality and vitamin D [6].

2.2.1 Diets

For factor diets, short durations of breastfeeding and early introduction of cow's milk may have a predisposing factor [6]. The benefit of breastfeeding is the additional protection by passing maternal antibodies, which may protect from potentially T1D-triggering exposures [6]. Moreover, according to one study, an elevated incidence of islet autoimmunity was linked to exposure to cereal during particular periods of early infancy [6]. Research also showed that increased intake of fatty acids can act as a protective factor [6].

2.2.2 Viruses

Since there are strong evidence linking viruses to T1D, they are thought to be one of the possible environmental triggers of the disease [6]. Viral infection by enteroviruses has been strongly considered as a potential disease trigger, but the exact mechanism of how it cause loss of pancreatic cells is uncertain [6].

2.2.3 Other Factors

There are clear links between T1D onset and seasons supported by research, and many reasons have been proposed, including the seasonal variation of blood glucose and insulin levels [6]. Increasing evidence also shows that vitamin D participates in regulation of immune response, which means vitamin D may related to the risk of T1D [6]. Vitamin D also has a positive effect in preventing T1D and this may related to its effect in modulating potentially pathogenic inflammatory processes [6].

3. Insulin Therapy

Insulin therapy is a typical traditional therapy. It replaces the insulin generated automatically by the human body and provides supplementation for T1D patients. It is generally divided into long-acting insulin therapy (which is also called basal insulin therapy) and rapid-acting insulin therapy (which is also called bolus insulin therapy). Some new insulin therapy is summarized in the following review.

3.1. Long-acting Therapy

New long-acting therapies include insulin glargine U-300 and degludec, which are also two kinds of ultra-long-acting insulin with faster action time. Insulin glargine U-300 has a more constant and evenly distributed glucose-lowering effect and a longer duration of action compared with insulin glargine U-100 [7]. It can maintain glucose control for 30h, which is much longer than glargine U-100 [7]. However, higher insulin requirement is needed to inject insulin glargine U-300 than insulin glargine U-100 [7].

Insulin degludec is an insulin analog with a glutamic acid and fatty acid side chain [7]. The glucose-lowering effect of its final injection lasts at least 42 hours after 8 days of once-daily injections [7]. Insulin degludec has four times lower day-to-day variability in glucose-lowering effect over glargine U-100 and extended duration [7]. Additionally, it demonstrated less nocturnal and normal symptomatic hypoglycemic episodes in the trial than insulin glargine [7]. It also shown less variation in the glucose-lowering effect over the day and during the day in a crossover analysis of 57 adult T1D patients [7].

The advantage of the two novel long-acting therapies described above is the potential to reduce the risk of diabetic ketoacidosis in patients with T1D [7].

3.2. Rapid-acting Therapy

New rapid-acting therapies include Fiasp and Afrezza. Fiasp, an improved version of insulin aspart, is an ultra-rapid-acting insulin therapy. It contains L-arginine, which increases stability, and vitamin B3 (niacinamide), which speeds up the rate of absorption [7]. It also has a faster appearance in venous blood, greater concentration, and greater insulin action in the first 30 minutes over insulin aspart [7]. When compared to insulin aspart, it offers superior postprandial glucose control [7]. Nonetheless, it shares certain negative effects with other rapid-acting insulins, including a marginally increased risk of postprandial hypoglycemia [7].

Afrezza insulin is an inhaled insulin made by Technosphere microparticles with dry powdered human insulin [7]. These particles can enter the deep lung through inhalation and swiftly dissolve into the bloodstream [7]. Despite its inferior glycemic efficacy relative to subcutaneous insulin, it presents a diminished risk of severe hypoglycemia and weight gain [7]. It can be used by patients who need rapid correction from hyperglycemia as it have a rapid onset of action [7]. However, it should not be used by smokers or people with lung conditions [7].

In summary, ultra-long-acting basal insulin therapy is distinguished by a reduced occurrence of nocturnal hypoglycemia and greater dosing flexibility, whereas the new rapid-acting insulin therapies are noted for their enhanced insulin efficacy and diminished hypoglycemia rates [7].

4. Novel Treatments

Researchers are finding therapies other than insulin therapy trying to treat or cure T1D. This includes stem cell therapy, immunotherapy and beta-cell replacement.

4.1. Stem Cell Therapy

Even though drugs and exogenous insulin administration can ameliorate hyperglycemia, they cannot provide physiological regulation of blood glucose [8]. Stem cell therapy becomes an alternative treatment to recover patients' insulin regulation in body.

There are different ways of using stem cells to treat T1D, including generating insulin-producing cells (IPCs), pancreatic progenitors, islets and interspecific pancreatic chimeras from different stem cells [8]. The procedure for creating IPCs with induced pluripotent stem cells (iPSCs) and embryonic stem cells (ESCs) will be covered in this review.

4.1.1 Generating IPCs

Since most current IPC generation techniques are focused on simulating normal pancreatic development, the produced IPCs ought to display particular biomarkers of normal beta-cells [8]. These indicators should be able to identify important functional characteristics of mature and terminally differentiated beta-cells, such as secretion of C-peptide [8]. In addition, they must respond to blood glucose fluctuations by generating adequate insulin and reverse hyperglycemia in the patient following implantation [8].

ESCs have infinite proliferative capacity, self-renewal and can differentiate into various types of adult cells in vitro [8]. However, it remain ethical concerns. ESCs and reprogrammed iPSCs can proliferate and differentiate similarly [8].

D'Amour et al. developed the first method for gradually cultivating endocrine hormone-expressing cells that can produce and release various hormones from hESCs in 2006 [8]. Nevertheless, the experimental outcomes were unsatisfactory. In differentiated hES cell cultures, the proportion of insulin-positive cells was low, and the polyhormonal cells showed little reaction to stimulation with high glucose levels [8]. Better outcomes are obtained when pancreatic endoderm cells are generated using an improved procedure and then transplanted into immunodeficient mice [8].

Rezania et al. made a breakthrough in 2014 with a more thorough procedure [8]. They were able to develop fully functional IPCs from hPSCs [8]. They divided the differentiation protocol into seven stages and obtained cells that expressed key markers of mature beta-cells, showing functional similarities to islets after transplantation [8]. In animal experiments, these cells can reverse hyperglycemia by secreting C-peptide and insulin [8]. However, due to the small and sluggish response of stage 7 cells to high glucose stimuli, these cells are still not equivalent to mature human beta cells [8].

Therefore, this therapy still faces significant challenges, such as how to produce more mature and functioning beta-like cells from hPSCs in vitro [8].

4.2. Immunotherapy

Experimental immunotherapy of T1D can be separated into nonautoantigen-specific and autoantigen-specific interventions [9]. Non-antigen (Ag)-specific methods include polyclonal Tregs, induction of tolerogenic dendritic cells (DCs), T-cell or B-cell depletion and immunosuppressive drugs [9]. Ag-specific approaches include adoptive transfer of Ag-specific Regulatory T-cells (Tregs), clonal deletion of effector T-cells and protein or peptide-based vaccines [9]. Combining those two methods to treat T1D is suggested, for the complexity of T1D pathogenesis.

4.2.1 Non-antigen-specific Immunotherapy

Non-Ag-specific immunotherapy aims to enhance immune regulatory systems in order to reduce harmful autoreactive immune responses [9].

Treg therapy is the most potential immunotherapy for autoimmune diseases including T1D. In T1D patients, their Tregs are impaired, so that their immune systems attack their beta-cells, leading to T1D. This therapy aims to recover the immune balance and protect beta-cells from destruction by giving Tregs cells. Polyclonal Tregs were isolated from T1D patients and grown ex vivo in a phase I clinical trial [9]. Then, the expanded polyclonal Tregs were transferred back into original patients [9]. It showed a fraction of polyTregs infused survived for several months [9]. C-peptide is produced when secreting insulin, so monitoring C-peptide levels showed that polyTregs can regulate the beta cell-targeted autoimmune responses effectively without serious side effects observed [9]. But these Tregs can show functional instability, and its production method is expensive and time-consuming [9].

4.2.2 Autoantigen-specific Immunotherapy

Autoantigen-specific immunotherapy for T1D abrogates islet beta-cell destruction by two methods. Inducing beta-cell-specific T-cell responses at ectopic sites and then growing Ag-specific Tregs, which subsequently gather in pancreatic islets is a method [9]. Another one is regulation of the balance between Teff and Tregs.

One way in autoantigen-specific immunotherapy is to modulate autoantigen-specific T cells. It can regulate the balance between Teff and Tregs. Efficiency can be increased by combining technological advancements in biomaterials and nanomedicines into process [9]. Nanoparticles coated with autoantigen-related MHC-II molecules were created by Santamaria and associates [9]. MHC-II is an important molecule participating in antigen presentation. Established autoimmune disorders can be addressed by these nanoparticles [9]. In addition, these particles have the ability to trigger and produce autoantigen-specific regulatory CD4+ T cells and to stimulate autoreactive T cells to differentiate into TR1 cells [9]. TR1 cells prevent autoimmune assaults and aid in reestablishing immunological tolerance. Additionally, these particles can stimulate and expand regulatory B cells, which in turn

stimulate CD4+ T cells and prevent T1D from progressing [9]. One major benefit of using nanomedicines is that they can avoid the demand for ex vivo Ag-specific Treg techniques [9].

4.3. Beta Cell Replacement

Cell therapy has the potential to be an autonomous, curative treatment for type 1 diabetes since the implanted cells can react to and control blood glucose levels [10]. However, the disparity between the availability and demand for human organs, as well as the need for lifelong immunosuppressive treatment to avoid immune-mediated graft loss and declining quality of graft mass partly due to the hostile implantation site are some of its limitations [10]. Thus, to accomplish long-lasting graft protection, the near-term development of this treatment aims to create an infinite supply of beta-cells, design the best implantation site, and apply targeted immunomodulatory strategies to address the aforementioned problems [10].

4.3.1 Sources of Beta-cell

For the limited number of human organ donors, researchers procure abundant beta cell resources for T1D [10]. Porcine islets can only be used in limited situation, as the body may be triggered immune attack the foreign [10]. Embryonic human pluripotent stem cells (ESCs), induced human pluripotent stem cells (iPSCs) and stem cell-derived beta-like cells (sBCs) are main beta cell resources that are research recently. It is theoretically possible for ESCs and iPSCs to self-renew quickly and specialize into any type of human cell [10]. However, ESCs remain ethical and HLA matching concerns [10]. Because iPSCs are derived from willing donors and can serve as a supply of autologous cells, they can allay these worries over ESCs. However, reproducible differentiation is still hampered by clonal diversity [10].

To create sBCs, there are two main approaches. The more developed one is implanting pancreatic progenitor (PP) cells and then differentiating them into sBCs by largely unknown in vivo-derived clues [10]. However, this process takes several months to achieve therapeutic functional mass and grafts show cellular heterogeneity, which needs to be improved in development of this approach [10]. Also, because of these unknown in vivo-derived clues, it may have some problems in aspects like differentiation.

Another approach is the sBCs production in vitro [10]. A definitive cell product at the time of transplantation, a reduction in graft volume, and the capacity to perform rapid graft function are its three primary benefits [10].

Static stimuli can cause glucose to react in vitro, however sBC cultures have a poor phenotype akin to that of immature newborn stages [10]. Altering the food supply and circadian entrainment may encourage maturation of sBC [10]. Multiple cell sources can be transdifferentiated into insulin-producing pancreatic beta cells, although this approach was not tested in human setting [10].

With blastocyst complementation, which uses patient-specific iPSCs to generate entire organs, beta-cells can also be produced [10]. Blastocyst complementation is a kind of gene editing technology that can help to recover lost function in body. By inhibiting native pancreas development, complementation with xenogeneic pluripotent cells can form a new pancreas within the vacant developmental niche [10]. However, growing chimeric human organs remains ethical concern and the ability to form a human pancreas has not been tested in humans yet [10]. Several issues remain plague the usage of sBCs, such as in vivo survival and functional immaturity [10].

4.3.2 Engineering Optimal Microenvironment

Engineering an optimal cellular transplant microenvironment can improve islet survival in vivo [10]. Features of the transplant microenvironment involve peri-islet extracellular matrix (ECM) and rich vascular network [10]. Even though different extrahepatic engraftment locations are studied, none of them are ideal for demanding organoids [10].

However, material-based approaches can help to improve its microenvironment by alleviating deficiencies of selected implant locations [10]. Subcutaneous channels made by temporary catheters can be utilized for cellular implant neovascularization and better nourishment [10]. Three-

dimensional (3D) biomaterials can be used to support healthy cell remodeling and islet revascularization [10]. Additionally, biomaterials enable graft extraction and provider site retention, which can lessen the safety risks associated to PSC-sourced implants because of the potential for non-terminal differentiation [10]. Additionally, materials could be altered to serve particular purposes in order to guide positive host and implant reactions [10].

4.3.3 Challenges Facing and Possible Solutions

A significant obstacle to beta-cell replacement therapies for the treatment of type 1 diabetes is the immunological reactions that transplanted islets may trigger, such as allogeneic immune identification and rejection and repeated autoimmune responses from the memory of pre-existing adaptive immunity [10]. But solutions are developing. CRISPR-Cas9 gene editing can help to escape natural killer cell-mediated killing by knocking out molecules [10]. Tregs can also potentially help to induce durable long-term tolerance [10].

5. Conclusion

Factors that contributed to T1D and four main therapies with their advances are summarized in this review, offering an overview for people who are interested in it. Insulin therapy is the main method used by T1D patients for its availability and maturity. And this therapy is continuously developing new insulin with higher effectiveness while novel therapies like stem cell therapy are focusing on how to completely cure T1D. However, deep researches are still needed to improve whether experimental or clinical results of novel treatments. For immunotherapy, it is hard to maintain long-term stability and functionality of beta-cell generated. So, it still cannot replace insulin therapy to cure T1D. Although beta-cells derived from the stem cell cannot replace normal beta-cell currently, its great result shows its potential and possibility of beta-cell replacement therapy. Beta-cell replacement face immunology challenges which can use immunotherapy to help to solve it. Stem cell therapy can also generate cells similar to mature beta-like human cells, but still have problems responding. Additionally, some current researches are tested on animals, so feasibility of therapies need to be discussed in the future. Thus, researchers can focus on combining different therapies against T1D and how to produce beta-cells in body with normal function.

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