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Current Technology and Biological Approach for Type 1 Diabetes Treatment

Kanjaree Suppawittaya*

Saint Joseph Convent School, Silom, Bang Rak, Bangkok, Thailand 10500
Email: 32495@sjc.ac.th

Abstract

Type 1 diabetes (T1D) is associated with immunity, especially human leukocyte antigens (HLA) class II loci. Insulitis forges inflammation and inhibits insulin-producing cells. As new devices are introduced, T1D patients' quality of life increases. Many types of insulin pumps make insulin administration easier. Hybrid insulin pumps (closed-loop systems) are found to keep blood glucose levels stable, improve HbA1c levels, and minimize diabetic ketoacidosis (DKA) occurrences. To improve the survival of islet grafts after transplantation, regulatory T cells (Tregs) have been used in immune treatments. When glucagon-like peptide 1 (GLP-1) receptor agonists are coupled with insulin, glucagon production is reduced and stomach emptying is delayed. Consequently, GLP-1 agonist medication appears to be effective in people with poor hemoglobin A1c (HbA1c) levels and obesity. Responding to islet stress, GLP-2 protects the endocrine pancreas. Human pancreas and islets transplantation may be a viable alternative for establishing long-term insulin independence; nevertheless, donor scarcity offers practical hurdles. Islet xenotransplantation is created to address this problem; however, there are still ethical grounds to consider. The use of neonatal porcine islet-like cell pancreatic cell clusters (NPCCs) has improved outcomes in preclinical investigations. Induced pluripotent stem cells (iPSCs) were constructed using somatic cells. Their limitless replication and capability to differentiate into functional-like cells provide great potential for creating glucose-responsive allogeneic cells for transplantation. Henceforth, advancements of cell encapsulation approaches and stem cell methods may strengthen graft survival. Established T1D therapy options must be further researched with novel therapeutic techniques to achieve the best clinical outcomes.

Keywords: Immunotherapy; insulin pump; peptide-based therapy; stem cell therapy; transplantation; type 1 diabetes.

1. Introduction

Diabetes can be classified into five different types in which two of those are type 1 diabetes (T1D) and type 2 diabetes (T2D), the main subtypes of diabetes [1, 2]. Although >85% of diabetes globally are T2D, the T1D rate of diagnosis is shown to increase at a constant pace of 3%-5% annually [2, 3].

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* Corresponding author.

To lessen the risks of further health complications in both microvascular and macrovascular endpoints, blood glucose levels should be strictly monitored and controlled, especially in early stages when the conditions are still manageable and the disease progression is yet to get out of hand [4, 5]. The destruction of β-cells, accompanied by CD4+ and CD8+ T cell activation, leads to T1D's pathogenesis, ultimately reducing beta cell mass [5-7]. In 1973, human leukocyte antigens (HLA) were identified to be related to insulin-dependent diabetes, however, not insulin-independent diabetes [8]. In other words, HLA is associated with T1D but not T2D [9, 10]. Since then, the immune system and T1D are found to have a close connection [3, 11]. Throughout the years, genome-wide association studies have reached a consensus that genes of HLA (specifically, HLA class II loci) determine approximately 50% chance of T1D's genetic risk [12-14]. This suggests that the pathogenesis of T1D is partly responsible by the specific autoantigen peptides' selective presentation [15-17]. This paper aimed to provide a comprehensive overview of current T1D technologies used worldwide and propose future directions of innovations and treatments towards the ultimate cure of T1D.

2. Etiology of T1D

Islet autoantibodies' seroconversion to insulin, insulinoma antigen 2, glutamate decarboxylase, or zinc transporter 8 are early indicators of autoimmunity in the progression of T1D [18, 19]. Assembled, they present the best determinant of both T1D's clinical manifestation and the body's loss of immune tolerance that comes with the presence of autoimmunity [6, 8]. However, it is rather unclear whether or not they take part in the destruction of β-cells [20, 21]. During T1D's development, insulitis is created by the immune cells' infiltration to the pancreas, thus targeting insulin-producing cells and forging inflammation [22, 23]. Presented by HLA class I molecules, insulitis increases islet antigens' exposure to the immune system, and stimulates T1D's progression [24, 25]. Clinically, the development of T1D is considered a complex process due to its muti-stages and multifaceted pathological factors [26]. T1D's adaptive immune system has been heavily studied upon through the analysis of peripheral lymphocytes on islet antigens' autoreactivity [15, 27]. According to studies, escalated persistence of islet-specific autoreactive CD8+ T cells and impaired regulatory immunological activity have been linked to the disease [17, 28, 29]. In the pathophysiology of T1D, T cells contribute extensively with the T1D's transfer after the transplantation of non-T-cell depleted allogeneic bone-marrow, T1D's progression in a B-lymphocyte and antibody deficient person, and T1D's emergence by deficit T-lymphocyte mechanism that the person genetically inherited [30, 31]. Majority of T1 diabetics' studies of peripheral autoimmunity illustrate that the public's phenotypes overlap [15, 32]. Furthermore, the periphery has only a tiny percentage of autoreactive cells. To put it another way, whereas there are millions of non-autoreactive cells, there are just a few autoreactive cells [3, 33]. Consequently, not much can be said about the relation between autoreactive immune cells in blood and T1D's development regarding islets [34]. However, many studies have shown that T1D's direct progression is due to the separation between T lymphocytes and islet donors with T1D's β-cell antigen peptides [35-37]. Looking into the histopathological facet, the mechanisms mentioned can be described as insulitis or immune-infiltrated (insulitic) islets. Although, in insulitic lesions, CD8+ T lymphocytes are typical immune cell types, CD4+ T cells could not be found as frequently as the prior [14, 38]. Different insulitis patterns in islets progress with the intensity of β-cell loss and the time period after diagnosis. Even though insulitis is prevalent in T1D model animals, it is uncommon in human beings [39, 40].

3. New devices for T1D

T1D is a lifelong chronic disease. Burdened by the intense level of care, the disease is associated with a poor quality of life (QoL) [41]. Despite many challenges people with T1D may face daily, technological advances, to an extent, have eased the burden and thus improved their well-being [41]. In short, recent medical advancement has significantly enhanced the QoL of those with T1D [41, 42]. For most T1D patients, self-monitoring of blood glucose (SMBG) is essential for disease management [43, 44]. Its functions include inserting finger-prick blood through a small channel in the test stript which is then plugged into the glucometer [45]. Subsequently, scientists developed continuous glucose monitoring (CGM) devices [46, 47]. Compared to the conventional SMBG devices, CGM devices are more preferred by the majority because of their advanced technology that enables rapid treatment decisions by monitoring his or her blood glucose level more frequently [48-50]. For instance, SMBG provides only snap-shots of blood glucose concentration, and is restricted by each person's number of daily finger-sticks [51, 52]. On the other hand, CGM can report up to 288 glucose values a day and depict temporal trends used to improve his or her glucose control [2, 53]. Moreover, the use of CGM devices decreases further complications after the diagnosis of diabetes since it notifies the conditions of hyper- and hypoglycemia [45, 48]. Thus, reduces the risks of fluctuating blood glucose levels and improves the overall QoL of people with T1D [54, 55].

4. Continuous subcutaneous insulin infusion

Insulin pumps, also known as continuous subcutaneous insulin infusion (CSII), were first introduced in 1963 and were carried in a large backpack [56, 57]. The first tiny wearable pump was introduced a decade later, marking the starting point of the process of insulin pump therapy [58, 59]. Diabetes-related technology has progressed steadily throughout the years [54]. Insulin pump therapy is now widely accepted as a viable therapeutic option for adults and children with T1D [60, 61]. An insulin reservoir is located inside the insulin pump [59, 62]. Rapid-acting insulin (175-300 units), including insulin aspart (novorapid) and insulin lispro (humalog), are stored in the insulin reservoir [62, 63]. Insulin pumps can be classified into three distinguished types which are tethered, patch, and implanted pumps [59]. In tethered insulin pumps, the most common form of insulin pumps, the reservoir is attached to the skin via an infusion set or a cannula, a small tube with a needle inside [64]. In patch pumps, there is nothing in between the pump and the skin. In other words, the pump is directly attached to the person’s body without an additional tube [65]. In implanted insulin pumps, the pump is internally implanted into the person’s body and insulin is delivered into the person’s peritoneal cavity [66]. This type of insulin pump is rarely utilized because it can only be refilled in a hospital center in Montpellier, France [67, 68].

5. Hybrid insulin pump (closed-loop systems) and the artificial pancreas

A recent attempt to adjust the delivery rate based on a person's blood glucose level fluctuation as sensed by the CGM has been a success [61, 62]. A new technique has been created to integrate a CGM sensor to a CSII, as well as the coordination of artificial intelligence technologies [50, 69]. Evidence-based concepts have been published, and small-scale trials with T1D individuals living independently with these devices have been

undertaken [69]. In 2017, the MiniMed 670G with Guardian Sensor 3 which is the first closed-loop system insulin pump was released by Medtronic [61, 70]. In March 2019, it was released in the United Kingdom [71]. Furthermore, in 'auto mode,' this hybrid device changes the insulin basal rates every 5 minutes based on the glucose levels monitored by the CGM to keep blood glucose levels tight and appropriate [46, 72]. Previous research has found that a person's HbA1c improves and that there are no cases of DKA or hypoglycemia in early safety trials [56, 73]. However, in the United Kingdom, eligibility is now highly limited [71]. At present, studies illustrate that releasing insulin glucagon bi-hormonal pumps can achieve near-normal glycemia, which reduces hypoglycemia and enhances time in glucose range [59, 61].

6. Immune therapies

The increase in T1D patients cannot be attributed exclusively to genetic predisposition [10]. It is widely acknowledged that self-reactive immune cells are activated by a combination of environmental stimuli and genetic vulnerability [74]. Consequently, the pathogenesis of T1D is complicated by the interaction of cells and constituents of both the adaptive and innate immune systems [75]. After activation, different cell types and various pathways are eliminated by the immune system [75]. Consequently, a number of immunomodulatory techniques have been devised to tackle the problems of T1D [75]. A significant clinical test was conducted, in the late 1980s, to determine cyclosporin A's therapeutic usefulness. Despite the fact that cyclosporin [76]. A treatment sustained T1D remission, research found that daily insulin requirement gradually increased [76].

Similarly, numerous clinical interventional trials using anti-CD3 and anti-CD20 monoclonal antibodies have shown simply transitory preservation of C-peptide levels [77]. A study that looked at the safety and effectiveness of antithymocyte globulin (ATG) discovered that it was unsuccessful to maintain cell activity after two years [77, 78]. A randomized controlled trial was also planned to assess the therapeutic efficacy of two renowned interleukin-1 (IL-1) inhibitors, Canakinumab (human monoclonal antibody against IL-1) and Anakinra (human IL-1 receptor antagonist) [79, 80]. Both Canakinumab and Anakinra imposed no harm but were ineffective as monotherapy for T1D's recent onset [31, 80]. The clinical trials' constant failures emphasize a knowledge gap that must be addressed before immunotherapies can be effectively translated for the benefit of people with T1D [31].

Currently, research is being conducted to produce the next generation of immunotherapies. Novo Nordisk is at present conducting a phase II clinical research with anti-IL-21 [32, 81]. Furthermore, an additional technique for modulating regulatory T cells (Tregs)'s activity is being thoroughly studied. It is well understood that regulatory T cells adversely regulate other functions of immune cells, including dendritic and cytotoxic T cells' [82]. Additionally, Tregs' immunomodulatory movement has been adopted to improve the survival rate of islet graft [83]. Preclinical inspections have indicated that animals co-transplanted with islets and Tregs without immunosuppression have longer islet life and function [21]. Tregs have been referred to by numerous human studies as a biological alternative to pharmacological immunosuppression and a potential strategy for modifying T1D patients' immune responses after islet transplantation [84]. Furthermore, autologous enhanced Tregs were found to be tolerable and safe in a modest clinical research including twelve newly diagnosed T1D children [85]. Using Tregs in treating patients, their inflammation is partially reduced and their maintenance of insulin

dosage is relatively constant during the two-year period [85]. *Ex-vivo* increased autologous Tregs' direct impact on functions of cells and is being studied by clinically ongoing dose-finding pilot research [86]. Current research has reported that, implementing a vigorous selection strategy concerning CD4 CD25 and CD127, isolating and expanding T1D patients' Tregs is practical [87]. To elaborate, Tregs had a higher functional activity when created in vitro, therefore the ex vivo enhanced Tregs were reintroduced into patients with T1D [87]. According to the data, injection Tregs lasted up to a year in ¼ of patients, and C-peptide feedbacks lasted up to a year in all cohorts and up to two years in two cohorts [88]. The same research group is now conducting a phase I trial combining Treg treatment with aldesleukin, a commercially accessible version of IL-2 [87]. Another innovative approach is to use nanoparticles, packed with pancreatic peptides that are covalently attached to the MHC-II protein, to target the immune system [16]. Nanoparticles coated with pancreatic peptides associated with MHC-II molecules linked to autoimmune illnesses are dispersed throughout the body using this technique. When mice are given coated nanoparticles, antigen-specific regulatory CD4(+) T cell type 1 (TR1)-like cells are activated and increased [89]. When coated nanoparticles were used, autoreactive T cells primed with peptides were shown to develop more quickly into type 1 regulatory (TR1) cells [29, 34]. TR1 cells repress autoantigen-presenting cells while encouraging cognate B cells to differentiate into disease-suppressive regulatory B cells [80]. The technique appeals to researchers because it focuses on the pancreas-specific immune response while ignoring the rest of the immune system [80].

7. Peptide-based therapies

Type 2 diabetes (T2D) and obesity are routinely treated with mimics of gut-derived peptide hormones, particularly glucagon-like peptide 1 (GLP-1) [90]. Preclinical research clearly demonstrates that several peptide hormones have beneficial effects and could be utilized to treat type 1 diabetes. Improved glucose control, insulin secretion, beta-cell mass preservation, cell apoptosis avoidance, and better insulin sensitivity are all part of this [90]. Clinical acceptance is the culmination of two decades of rigorous preclinical studies [90]. The therapeutic potential of GLP-1 receptor agonists as a complement to T1D patients' insulin therapy has been investigated in several exploratory clinical trials [91]. As insulin is combined with the GLP-1R agonists exenatide and liraglutide, the results demonstrate a significant decrease in postprandial glucose excursions, a decrease in glucagon production, and a delay in stomach emptying when compared to insulin alone [91]. In addition, pairing an anti-IL-21 antibody with liraglutide improved glycemic control in diabetic mice, according to a study [91]. In a clinical proof-of-concept research, anti-IL-21 in conjunction with liraglutide is now being investigated in newly diagnosed T1D patients [91]. As a result, GLP-1 agonist therapy appears to be beneficial in people with unmanageable HbA1c and moderate obesity [91]. Nonetheless, the long-term effects of GLP-1-based medicines on glycemic management and consequences are uncertain [91].

Oxyntomodulin (Oxm) is a hormone generated in the gut that functions by activating both the GLP-1 and glucagon receptors at the same time [92]. Oxm appears to be involved in cell function as well. Because of concomitant glucagon receptor activation, using Oxm as an adjuvant therapy to insulin in the treatment of T1D appears contradictory [92]. In a mouse study, however, oxym monotherapy resulted in a considerable decrease in circulating blood glucose and an increase in the number of tinier islets. The peptide hormone glucagon-like peptide 2 (GLP-2) is produced by L cells in the intestinal endocrine in response to food intake. GLP-2 appears

to protect the pancreas, particularly when islet stress is present [93]. GLP-1 and GLP-2, which are generated from pro-glucagon, have previously been discovered to colocalize with peptide YY (PYY), which is secreted by intestinal L cells. PYY expression in islets, pancreatic polypeptides, and cells is rare [94]. PYY is hypothesized to have a contribution in the direct regulation of islet cell activities like insulin secretion and beta-cell mass maintenance as a result of this [94]. According to the study, peptide hormones play a significant role in islet cell activity and stress response modulation [94]. The therapeutic potential of peptide hormone-based T1D therapy is highlighted by these findings [91, 94].

8. Islet transplantation and Xenotransplantation of Islet

Exogenous insulin can be replaced via islet transplantation [84]. Prior to the discovery of insulin, the first attempt at xenotransplantation was made in 1893 [80]. In 1972, Ballinger and Lacy employed isolated islets to reestablish glycemic control in streptozotocin-induced diabetic rats via the intraportal vein [80]. The successful intraportal transplantation of patients with their islets followed in 1980 [80, 95]. Three people achieved total insulin independence after 1, 9, and 38 months, according to the researchers [96]. Additionally, using the Ricordi chamber to construct a semi-automated islet separation method to improve the islet isolation protocol allows for more efficient islet transplantation while lowering islet loss [97]. Since then, the Ricordi chamber has remained the best model for islet separation from the human pancreas [80, 97]. Human pancreas and islets transplantation is a potential option for achieving insulin independence for the rest of one's life; nevertheless, donor scarcity poses practical challenges [97]. Islet xenotransplantation shows a lot of potential for addressing the donor scarcity. The first attempt at transplanting pig islets into humans with type 1 diabetes occurred in 1994 [97]. C-peptide levels were found in the urine of patients for up to 300 days after transplantation [98]. These, on the other hand, had no evident effect on blood glucose levels. Several small clinical studies have since been published that show the benefits of employing pig-derived islets to treat type 1 diabetes. T1D treatment has been shown to have significant clinical benefits in several studies. Finding a dependable supply of pig islets, devising a procedure for immunological xeno-islets isolation, and selecting adequate transplantation stations are all obstacles to practical adoption of this strategy. The use of neonatal porcine islet-like cell pancreatic cell clusters (NPCCs) rather than adult islets has been shown to improve outcomes in preclinical investigations. This includes a high rate of survival after islet isolation prior to transplantation, especially in an ischemic ex vivo setting. Furthermore, the encapsulated NPCCs proliferate and grow into mature cells following transplantation, allowing for excellent glucose regulation. NPCCs, like mature islet cells, are defiant to the fatal effects of pro-inflammatory cytokines produced by the host, including as interleukin-1 (IL-1), tumor necrosis factor-alpha (TNF- α), and interferon-gamma (IFN- γ). To lessen the risk of zoonosis from porcine grafts, a multitude of pathogen-free pig breeds are available, including New Zealand Auckland Island pigs, Chicago Medical School micro pigs, and transgenic pigs targeting porcine endogenous retrovirus (PERV) [98].

Furthermore, utilizing genetically altered xeno-islet grafts, several trials have shown consistent glycemic control [84]. Islets that were genetically modified to excessively make copies of the anti-apoptotic gene *Bcl-2*, for example, were transplanted and showed a stable, functional profile with negligible islet loss [80]. Pigs expressing human antithrombotic or anticoagulant genes such thrombomodulin, tissue factor pathway inhibitor, or CD39 can also help lower the instant blood-mediated inflammatory reaction (IBMIR) and improve

transplantation results [99]. In the future, genetically engineered pigs with particular expression patterns for genes involved in immune regulation, survival, and function may be used to improve transplant outcomes [99]. Before islet xenotransplantation can be widely employed, other difficulties such as transgenic pigs' genetic stability and ethical consideration must be addressed [99].

9. Induced pluripotent stem cells therapy

Induced pluripotent stem cells (iPSCs) were created using somatic cells. Using autologous iPSC technology, several patient-specific iPSCs have been converted from adult somatic cells into functional cells. T1D-specific iPSCs have been produced from T1D patients using the Yamanaka factors Oct3/4, Sox2, c-myc, and Klf4. In addition, significant progress has been made in the understanding of critical signaling networks and regulators that ensures effective cell functioning. The transplantation of glucose-responsive and insulin-producing pancreas progenitor cells into mice was the culmination of these efforts. Furthermore, iPSC-derived cells display mature cell-like markers like PDX1, NKX6.1, MAFA, PCSK1, and PCSK2, which protect diabetic mice from T1D progression.

These iPSCs provide great potential for creating glucose-responsive allogeneic cells for T1D patients' transplantation due to their limitless replication ability as well as capability to differentiate into functional-like cells. Furthermore, the potential of iPSCs to create autologous TGF-1 and IL-10-producing Tregs improves its usage in T1D therapy [100]. As a result of the extensive research, the clinical utility of using the iPSC technique to create a patient's cells will be determined. There are also some additional benefits to using iPSCs over human embryonic stem cells (hESCs), such as fewer ethical concerns [21, 100, 101]. Additionally, iPSC technology has advanced to the level where patient-specific iPSCs can now be employed as a major supply of autologous cells for cell therapy without the risk of immunological rejection [21]. This, along with genome modification for gene repair, bodes well for T1D treatment [21]. Cell generation from iPSCs, on the other hand, is a difficult procedure that necessitates the coerced expression of transcription factors to match the pancreas' typical maturation stages [21]. Furthermore, iPSC-derived cells, according to gene expression analyses, lack the features of full grown cells and are more akin to embryonic cells [21, 101]. In addition, there is a lot of evidence that iPSC-derived transplanted grafts can cause teratomas in the body. The costs of adequate manufacturing procedures for stem cell synthesis and reprogramming per patient could restrict the procedure's overall viability [21]. All of these roadblocks to iPSC-derived cell therapy clinical translation remain significant [100, 101].

10. Future perspectives

T1D continues to be a significant cause of kidney failure, blindness, and stroke. The number of instances has continuously climbed during the last four decades [102]. While the recent release of fast-acting and long-acting insulin analogues has enhanced T1D patients' quality of life, there are still certain hurdles to overcome [102]. Primary islet transplantation has a lot of promise for treating T1D patients [102]. The scarcity of islets, on the other hand, remains to be a substantial barrier to the widespread use of islet transplantation. Islet xenotransplantation has been considered as a solution to donor scarcity [80]. However, there are still ethical concerns and concerns regarding the genetic stability of transgenic islets. As a result, insulin replacement

therapy and human islet transplantation remain viable and financially sustainable choices for treating T1D for the time being [80]. Numerous hurdles, including significant islet cell loss during the immediate post-transplantation phase, obstruct the development of viable human islet transplantation techniques. As a result, the count of islets required to achieve sufficient glucose management and insulin independence climbs exponentially [80]. Furthermore, disturbance of normal islet construction and shape, as well as inadequate vascular engraftment, contribute significantly to graft function deterioration during the post-transplantation period [4]. During the early post-transplant phase, isolated islets were exposed to severe shear pressures, which resulted in a decrease of beta-cell quantity and function, eventually leading to graft failure [4].

To obtain best treatment outcomes and ultimate insulin independence, new tactics are necessary [4]. The advancement of cell encapsulation approaches and stem cell methods such as islet mobilization and implantation in conjunction with ECFCs and/or MSCs may strengthen graft survival by aiding with revascularization and providing paracrine growth factors necessary for propagation and operation to both pre- and post-transplanted islets [103]. Established T1D therapy options such as insulin substitution, immunological therapies, SGLT2 inhibitors, and peptide agonists must be researched alone or in combination with novel therapeutic techniques to achieve the best clinical outcomes [80, 104]. Through further studies on these novel approaches to tackle T1D, they are in all likelihood to become promising therapies that will enhance T1D patients' quality of life.

11. Conclusion

In recent years, the number of technologies available for managing T1D has expanded dramatically. T1D is a major personal burden that has a negative impact on both the quality and quantity of life. Innovative technologies could make a huge difference in how this challenge is managed. The convenience of glucose testing has been an important target of therapy for many years, and it has finally realized its promise. In many patients, CSII insulin administration is a well-established therapy with unique benefits for avoiding hypoglycemia and improving glucose control. The introduction of closed-loop devices, which may offer the advantages of lowering the patient's burden of care and minimizing the likelihood of adverse events, is on the verge of a paradigm shift in T1D therapy. While these technologies are now pricey, they are expected to grow less so as the technology becomes more widely available. There is little evidence that these devices effectively minimize T1D difficulties at this time. If their utility can be fully shown, these technologies' cost-effectiveness will almost likely be high, and the innovative approaches' adoption will certainly accelerate.

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