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EMERGING THERAPEUTIC STRATEGIES FOR TYPE 1 DIABETES

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Modern medical research identifies type 1 diabetes mellitus (T1D) as one of the most pressing global health challenges, with the incidence steadily increasing by up to 500,000 new cases annually. Current treatment approaches do not provide optimal glycemic control, as they are mainly aimed at compensating for endogenous insulin deficiency, which can significantly compromise patients' quality of life. For a long time, researchers have sought a treatment strategy capable of achieving a rapid, safe, and reliable cure for T1D. Yet, due to the insufficient understanding of the mechanisms driving the autoimmune response underlying this condition, modern medicine has not been able to develop an etiotropic therapy that could ensure complete recovery. A wide range of therapeutic developments targeting different pathogenetic mechanisms of T1D are currently underway, all aimed at supporting optimal glucose metabolism. Their objectives include preventing or slowing disease progression (delaying the onset of the clinical stage) and facilitating glycemic control in affected patients. Despite substantial progress, none of these innovative strategies has yet reached widespread clinical application. The primary obstacles remain the lengthy timelines required to complete full cycles of clinical trials and the need to address limitations revealed during the research process. This review presents the leading modern approaches to T1DM therapy, with a focus on insulin therapy, immunotherapy, and cell-based strategies. Clinical trial data are analyzed, highlighting both advantages and limitations from practical and economic perspectives. The approaches discussed represent the most promising avenues and are expected to play a central role in future treatment of T1DM.

Keywords: type 1 diabetes mellitus, pancreas, immunotherapy, cell therapy, insulin therapy.

INTRODUCTION

Type 1 diabetes mellitus (T1D) is a polyetiological, multifactorial disease, the central mechanism of which involves an autoimmune response triggered by genetic predisposition in combination with various environmental factors. As a result of this immune-mediated aggression, pancreatic beta cells are destroyed, leading to an absolute insulin deficiency.

TID is considered a socially significant disease, with its incidence growing steadily worldwide. According to the Russian Federal Diabetes Registry, as of 2023, the number of patients with TID in Russia reached 277,100, representing 5.58% of the total diabetes population [1].

At present, the standard method of replacement therapy for T1D – insulin therapy – remains widely used in clinical practice. The introduction of modern insulin formulations, pump insulin therapy, continuous glucose monitoring systems, and closed-loop technologies has improved glycemic control in many patients. However, this approach often has low effectiveness due to its high resource intensity, requiring considerable time, concentration, and clinical expertise to demonstrate target therapeutic indicators.

Conventional insulin therapy also imposes significant lifestyle restrictions, particularly regarding diet and physical activity, and the use of repeated injections in conjunction with the complex pharmacokinetics of insulin preparations frequently results in suboptimal glycemic control. This is reflected in the high incidence of severe hypoglycemic episodes and the continued progression of late complications associated with chronic hyperglycemia, such as diabetic neuropathy (41.3%), diabetic retinopathy (28.9%), and diabetic nephropathy (22.8%) [2].

Over the past few decades, numerous efforts have been made to address the existing limitations of insulin therapy through transplantation-based technologies. Approaches such as isolated and combined pancreas–kidney transplantation, xenotransplantation, allotransplantation, and autotransplantation of pancreatic islet cells have been explored and continually refined. However, these methods are characterized by limited efficacy, frequent postoperative complications, and a dependence on immunosuppression, which restrict their application to severe clinical cases.

Current research trends focus on optimizing existing transplantation approaches and developing novel therapeutic strategies aimed at preventing disease onset and

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slowing or halting the progression of late complications. The genetic contribution to disease susceptibility and the precise mechanisms underlying the autoimmune response in TID remain incompletely understood.

Modern technologies, particularly those targeting specific pathogenetic pathways, are now being actively investigated. Several of these experimental strategies have already shown promising results in clinical trials, suggesting the potential not only for significantly improved disease control but also for the achievement of long-term clinical remission in T1D patients.

INSULIN THERAPY

Insulin therapy remains the gold standard for managing T1D. The classic treatment regimen involves daily administration of basal insulin, supplemented by bolus injections of short-acting insulin before meals. This section discusses modern strategies aimed at overcoming the limitations of conventional insulin therapy, forming the foundation for the development of next-generation insulin formulations.

Speed of activation and duration of action

The use of bolus insulin prior to meals requires a certain pause. Modern ultra–short-acting insulin analogues, which exist primarily in hexameric conformation, exhibit a delayed onset of pharmacological effect – usually 5 to 15 minutes after injection. This pharmacokinetic lag restricts their clinical flexibility and can contribute to postprandial hyperglycemia in patients with T1D.

To address these challenges, ultra-rapid short-acting insulin analogues have been developed. These formulations consist of shorter insulin molecules that achieve faster absorption and earlier metabolic activity, thereby mimicking the physiological profile of endogenous insulin secretion more closely. A promising example of this class is AT247 (Arecor Therapeutics plc, UK), an ultra-rapid insulin analogue. In Phase I trials [3], AT247 demonstrated superior glycemic control compared with traditional short-acting analogues such as insulin aspart, due to its accelerated absorption (onset of action within 1–10 minutes) and optimized pharmacokinetic–pharmacodynamic characteristics.

Current trends in the development of basal insulin formulations are focused on creating long-acting analogues that require only once-weekly administration. Their prolonged duration of action is primarily attributed to enhanced binding affinity to serum albumin. Such formulations not only improve treatment convenience but also promote more stable glycemic control, as they lack a pronounced peak of activity.

A notable example is insulin icodec (Novo Nordisk, Denmark), which has been approved for clinical use in Canada. Its extended pharmacokinetic properties result from specific structural modifications, including the replacement of three amino acid residues, leading to a half-life of approximately 196 hours [4]. Clinical trials have demonstrated its therapeutic equivalence to insulin degludec, although a higher incidence of hypoglycemic events has been reported, necessitating individualized dose adjustment [5].

Another promising once-weekly basal insulin currently in development is efsitora (Eli Lilly, USA). In clinical studies, efsitora has shown a reduced frequency of nocturnal hypoglycemic episodes and a decreased requirement for short-acting insulin compared with insulin degludec [6].

Glucose-sensitive insulins

Patients with T1D must not only coordinate insulin injections with meals but also adjust doses according to physical activity, which can precipitate hypoglycemia. The development of glucose-sensitive "smart" insulins, which activate only under hyperglycemic conditions and become inactive once physiological glucose levels are restored, offers a potential solution. These formulations more closely mimic endogenous glucose regulation, enabling optimized glycemic control while minimizing the risk of hypoglycemia.

A promising advance in this area is the creation of an oral glucose-sensitive insulin, which eliminates injection-related challenges. This formulation exhibits glucose-dependent activity and consists of insulin complexed with a silver compound and a chitosan–glucose polymer coating. The coating protects the insulin molecule from acidic gastric degradation, maintaining its bioactivity as it transitions into the alkaline environment of the duodenum [7]. After intestinal absorption, insulin accumulates in hepatocytes, forming a metabolic depot. Under hyperglycemic conditions, enzymatic cleavage of the complex triggers a controlled release of insulin into the bloodstream, achieving dose-dependent effect without the risk of hypoglycemia.

An alternative technological approach to glucose-responsive insulin delivery involves the creation of insulin conjugates with amphiphilic polymers, in which surface charge modulation enables glucose-dependent insulin release. Following oral administration, these micellar nanostructures are efficiently absorbed in the gastrointestinal tract and transported via the portal circulation to the liver, where they form a metabolic depot [8].

The rapid activation of insulin when blood glucose rises is most similar to the physiological synthesis of insulin by the pancreas. The drug is in the preparation stage for clinical trials, demonstrating stable 24-hour glycemic control while maintaining a high safety profile in preclinical studies on animal models.

Insulin pump therapy

Patients with T1D are most often children or young adults who lead active lifestyles, which significantly influences blood glucose variability and necessitates frequent monitoring and dose adjustment. Insulin pump therapy has become increasingly prevalent as a means of achieving a more physiological glycemic profile. These devices enable precise, programmable insulin delivery, allowing hourly dose adjustments tailored to individual needs. This flexibility is particularly beneficial for managing phenomena such as the "dawn phenomenon" and for delivering extended boluses during prolonged food intake.

There are now closed loop systems (CLS) that integrate an insulin pump, a continuous glucose monitoring (CGM) device, and an automated control algorithm – embedded either within the pump or as a separate module – to analyze CGM data and regulate insulin delivery with minimal user intervention. In parallel, non-commercial open-source systems, such as DIYAPS (Do-It-Yourself Artificial Pancreas Systems), have emerged. These user-driven platforms operate outside traditional regulatory frameworks and are based on publicly available algorithms that can be customized to individual preferences [9].

The implementation of such technologies aims to enhance patients' quality of life by reducing the cognitive and emotional burden associated with routine glucose monitoring and carbohydrate counting (CC). Clinical studies have shown that the use of closed-loop and open-source systems reduces both the risk and frequency of hypoglycemia and increases the percentage of time spent within the target glucose range [10].

However, current closed-loop insulin delivery systems remain technologically imperfect, with several key limitations related to the lack of integration of parameters that modulate the glycemic profile, such as as heart rate, sweating intensity, physical activity levels, and the rate of gastrointestinal nutrient absorption. This factor necessitates periodic manual recalibration of algorithmic settings, thereby precluding their static use without dynamic monitoring.

A clinical case reported by Ametov et al. [11] highlights the potential risks of improper system configuration. The case involved a patient using an unregulated AndroidAPS (AAPS) platform paired with an Accu-Chek insulin pump (Roche, Switzerland) and a FreeStyle Libre 1 continuous glucose monitoring system (Abbott, USA). After two years of use without algorithmic adjustment, the patient was hospitalized with severe hypoglycemia precipitated by alcohol consumption without corresponding insulin dose modification.

Current closed-loop insulin delivery systems are not yet fully autonomous, and patient participation remains essential for effective glycemic control and the maintenance of carbohydrate metabolism compensation. Given the continued need for user oversight, the impact of these systems on quality of life remains a subject of debate. While several studies have reported improvements in patient-reported outcomes, findings across the literature are inconsistent.

According to a meta-analysis by X. Jiao et al. [12], when comparing closed-loop systems with conventional methods such as standard insulin pump therapy and multiple daily injections, no statistically significant differences were observed in quality-of-life measures or diabetes-related distress. The authors suggested that the potential benefits of closed-loop systems may be offset by the challenges associated with understanding and operating complex technological interfaces.

A promising direction for future research is the development of fully autonomous bihormonal systems, which combine the delivery of insulin with glucagon (or, in some designs, pramlintide) to replicate physiological pancreatic regulation. However, a 2022 meta-analysis by B. Zeng et al. [13] revealed that, despite a reduction in hypoglycemic events, bihormonal systems achieved no significant improvement in time-in-range compared with single-hormone analogues and were associated with an increased incidence of gastrointestinal side effects.

Alternative routes of insulin administration

A major limitation of conventional subcutaneous insulin therapy is the occurrence of local injection-related complications, including lipodystrophic tissue changes and, in some cases, abscess formation. To mitigate these adverse effects, research has focused on alternative routes of insulin administration, with oral and inhalation formulations emerging as the most promising options.

The oral route offers several advantages, being both safer and more physiologically relevant. It mimics the natural pathway of endogenous insulin, which first passes through the hepatoportal circulation, ensuring primary hepatic exposure similar to insulin secreted by pancreatic beta cells. Numerous oral insulin formulations have been developed to overcome challenges such as acidic degradation in the stomach and enzymatic cleavage, as well as to enhance intestinal absorption. Notable examples include ORMD-0801 (Oramed Pharmaceuticals, Israel), I338 (Novo Nordisk, Denmark), and IN-105 (Biocon Limited, India) [14].

An innovative advancement in this field is the self-orienting microdelivery applicator (SOMA) – a miniature autonomous system for targeted insulin delivery to the gastric mucosa [15]. SOMA consists of a microneedle containing insulin and a compressed spring encapsulated in a sugar-based coating. The device is engineered such that its center of gravity aligns with the needle tip, enabling proper orientation within the stomach. Upon dissolution of the sugar coating by gastric fluid, the spring

mechanism is activated, inserting the insulin-loaded needle directly into the gastric wall.

A promising advancement in the optimization of T1D therapy is the development of inhaled insulin formulations, the most notable of which is Afrezza (MannKind Corp., USA) – currently the only inhaled insulin approved for clinical use. Afrezza is an ultra–short-acting insulin designed for use in combination with long-acting basal analogues to control postprandial hyperglycemia.

This delivery route enhances the efficiency of insulin absorption by providing a large surface area of contact with the drug, which enters the systemic bloodstream and acts within 30 minutes. Clinical studies have demonstrated that Afrezza significantly reduces the frequency of hypoglycemic episodes compared with insulin lispro, although coughing has been reported as a common side effect [16].

A major advantage of inhaled insulin is the ability to provide postprandial glucose correction without the cumulative effects or prolonged activity associated with subcutaneous injections, owing to its short half-life and rapid clearance [17, 18].

Other methods of insulin administration are being developed, but they have not yet been fully studied or have certain disadvantages from a practical and economic point of view (Table).

Hepatic-directed insulin

Another innovative approach in insulin therapy is the hepatic-directed vesicle insulin (HDV) system, designed to target insulin delivery directly to the liver. This technology utilizes vesicular microdisks that facilitate the transport of insulin – regardless of its route of administration – to hepatocyte receptors.

Under normal conditions, pancreatic insulin reaches the liver via the portal venous system, where a portion is inactivated to prevent hypoglycemia, while the remainder promotes hepatic glucose uptake and suppresses hepatic glucose production, effectively preventing postprandial hyperglycemia. Peripheral insulin administration results in a reduced proportion of hepatic glucose utilization and an increased uptake by muscle tissue, leading to glycogen depletion and a greater risk of hypoglycemia [23].

The HDV system aims to restore this physiological distribution, thereby normalizing hepatic and peripheral glucose metabolism. Its use has been shown to reduce nocturnal hypoglycemia, improve glycated hemoglobin levels, and enhance overall glycemic stability. Clinical trials of HDV–insulin lispro (HDV-L) showed both improved glycemic control and a lower incidence of hypoglycemic episodes compared with conventional insulin lispro [24]. Additionally, the insulin delivery system to the liver helps to increase the rate at which it starts working and reduce the required doses.

IMMUNOTHERAPY

One of the key mechanisms in the pathogenesis of T1D is the autoimmune reaction directed against pancreatic β cells and molecules involved in insulin metabolism. T cell–mediated immune aggression, together with the production of autoantibodies, plays a central role in this process. The clinical course of T1D progresses through three distinct stages [25]. In the first stage, the autoimmune process begins, characterized by the appearance of specific antibodies in the blood. Stage 1 diabetes is defined by the presence of at least two of five possible autoantibodies: ICA (against β cells), anti-GAD (against glutamate decarboxylase), anti-IA-2 (against

Table

Alternative insulin delivery routes [14]

Delivery route	Drugs	Characteristics
Intranasal	1. Cell-penetrating peptides 2. Chitosan 3. Ammonium salts	Administering insulin via these routes effectively lowers blood glucose levels. The use of molecules that enhance cell membrane permeability can improve insulin absorption and glycemic control.
Buccal	PharmFilm (MonoSol; Midatech, USA; UK)	A promising minimally invasive method of administering insulin in the form of a rapidly dissolving mucoadhesive film. These films have a rapid onset of action due to the rich vascularization of the oral cavity [19]. Undesirable effects include mucosal irritation and discomfort, which can lead to inadvertent swallowing of the drug.
Transdermal	1. Microneedles for insulin delivery 2. Jet insulin injector 3. U-Strip patch (Dermisonics, Inc., USA)	A potentially promising route of insulin administration due to its minimal invasiveness. Studies have shown its effectiveness, safety, and patient preference over parenteral forms of insulin [20]. Current research is focused on improving insulin transport through the skin and enhancing bioavailability.
Rectal	1. Labrazol 2. HPMC-co-PAM-co-PMAA hydrogel	The advantages of this method of insulin administration are rapid and relatively complete absorption into the systemic circulation [21]. The drug bypasses the harsh gastric environment, although the presence of a pronounced mucosal barrier can reduce efficacy. Various enhancers can be used to improve insulin delivery via these routes [22].

tyrosine phosphatase), IAA (against insulin), and ZnT8 (against zinc transporter 8). At this point, β-cell function and blood glucose levels remain normal. In the second stage, progressive autoimmune destruction of β cells results in impaired glucose tolerance or impaired fasting glycemia. The third stage corresponds to the clinical manifestation of T1D and the need for insulin to maintain normal glucose levels.

T1D has a fairly long preclinical phase characterized by progressive autoimmune destruction of pancreatic β cells. Modern immunomodulatory therapies selectively target key components of the pathological immune response, helping to preserve the residual function of insulin-producing cells and prevent the onset of absolute insulin deficiency. Administering such therapies during stages 1 and 2 can delay the clinical manifestation of T1D. Moreover, studies have shown that some patients retain residual insulin secretion even years after diagnosis [26], and immunotherapy in these cases can significantly improve glycemic control.

Most immunotherapeutic strategies aim to enhance the activity of regulatory T lymphocytes, suppress autoreactive T cells, or reduce autoantibody production by B lymphocytes. However, many existing approaches require prolonged use of non-selective drugs that deplete immune cells and cause immunodeficiency, limiting their widespread use. Therefore, increasing attention is being directed toward new selective immunomodulatory agents that are currently in development or already in clinical use.

Several studies have demonstrated that functional or quantitative deficiency of regulatory T cells (Tregs) plays a critical role in the pathogenesis of T1D [27], leading to uncontrolled activation and proliferation of autoreactive T lymphocytes. Targeting this mechanism helps induce stable immunological tolerance to pancreatic islet antigens, which clinically manifests as stabilization of glycemic control and improved metabolic regulation.

Correction of Treg deficiency can be achieved through two main approaches: transplantation of Treg cell material in cases of absolute deficiency, or activation of the endogenous Treg pool via antigen-specific immunization with islet antigens. A key prerequisite for therapeutic success is the selective suppression of autoimmune responses directed specifically against β-cell antigens, thereby minimizing systemic immunosuppression. The most promising strategies involve avoiding broad, non-specific Treg activation – instead focusing on generation of *ex vivo*–optimized Tregs for reinfusion into patients or direct *in situ* stimulation [28].

Immunotherapy targeting quantitative Treg deficiency

This type of immunotherapy aims to compensate for quantitative Treg deficiency through cell-based approaches. One strategy involves *ex vivo* autologous transplantation of expanded Tregs. Modification of these cells before reinfusion enhances therapeutic efficacy while avoiding the need for systemic immunosuppression. Clinical studies assessing the safety and efficacy of this approach have reported no clinically significant adverse events [29].

Within two years following therapy, patients demonstrated increased C-peptide levels and reduced requirements for exogenous insulin, with two cases achieving complete insulin independence [30]. Optimization of outcomes using polyclonal Tregs can be achieved by combining this approach with low-dose interleukin-2 (IL-2) therapy [31]. Experimental evidence suggests that this combination expands both transplanted and endogenous pools of functionally active Tregs and enhances their survival; however, it may also stimulate the proliferation of cytotoxic cell populations.

Ex vivo therapy using expanded polyclonal Tregs, PTG-007 (PolTREG, Poland), has demonstrated high therapeutic efficacy. In patients with early-stage T1D, this treatment resulted in insulin independence lasting up to 24 months and reduced insulin requirements for up to 12 years [32]. The combined use of Tregs and Rituximab has proven to be the most effective.

However, a key limitation of *ex vivo*–expanded Treg therapy is the potential phenotypic instability of these cells, which may lead to their transformation into pathogenic autoreactive effector T cells. Therefore, long-term monitoring of T-cell specificity is essential, along with rigorous *in vitro* quality control before reinfusion into patients.

Preclinical studies in experimental animal models indicate that antigen-specific Tregs provide superior therapeutic efficacy compared to polyclonal populations [33]. Nonetheless, the technological challenge lies in isolating these antigen-specific cells, as they are predominantly localized within the target tissue – the pancreatic islets.

Immunotherapy targeting Tregs quality deficiency

There is an alternative therapeutic approach that offers significant advantages in terms of cost-effectiveness and clinical feasibility compared to *ex vivo* cell-engineering techniques. *In situ* antigen exposure stimulates the activation of antigen-specific Tregs directly within target tissues, thereby enhancing immune tolerance.

Recent advances in bioengineering have enabled precise targeting of immune components, site-specific drug delivery, and controlled release mechanisms [34]. For instance, gold nanoparticles can serve as delivery vehicles, carrying proinsulin peptide molecules as autoantigens to induce antigen-specific tolerance [35]. Another promising delivery platform involves genetically modified strains of Lactococcus lactis engineered to produce hu-

man proinsulin and interleukin-10, thereby promoting antigen-specific immunological tolerance [36]. Monotherapy with AG019 (Precigen ActoBio, Belgium) has led to reduced HbA1c levels and a 24% increase in C-peptide six months after administration [37].

One of the most studied therapeutic strategies for T1D is antigen-specific immunotherapy using GAD-alum (Diamyd), developed by Diamyd Medical (Sweden). This approach employs recombinant human GAD65 protein, a major islet autoantigen. The mechanism of action involves the induction and expansion of regulatory T cells (Tregs), which helps preserve and enhance the residual functional activity of pancreatic β cells. Clinical efficacy has been demonstrated in patients with newly diagnosed T1D (within 6 months of onset) who are GAD65-seropositive and carry the HLA DR3-DQ2 haplotype. The therapeutic regimen includes three intralymphatic injections into the inguinal lymph nodes, administered at monthly intervals, in combination with vitamin D supplementation [38].

Clinical studies have reported lower mean glucose levels, reduced frequency of hyperglycemia episodes, and longer durations within target glycemic ranges over a 15-month follow-up period. Preservation of endogenous insulin secretion was observed in a substantial proportion of patients for 30–43 months. One observation documented sustained β-cell functional activity for up to 8 years following treatment. Current investigations are assessing the use of booster doses administered 31.5 months post-therapy to extend the duration of clinical benefit [39].

Another promising therapeutic approach for T1D is IMCY-0098 Imotope (Imcyse SA, Belgium), designed to slow disease progression and prevent early onset of T1D. This compound is a linear synthetic peptide incorporating the C20-A1 epitope of proinsulin. Its mechanism of action involves the induction of $CD4^+$ regulatory T-cell proliferation, leading to targeted elimination of antigen-presenting cells and autoreactive effector T lymphocytes involved in pancreatic β-cell destruction [40]. Preliminary clinical trial data have demonstrated a favorable safety profile, and ongoing studies are assessing the therapeutic efficacy of this approach [41].

Immunotherapy targeting T-cell immunity in general

One of the most studied agents in this class is Teplizumab (Provention Bio Inc., USA), a humanized monoclonal antibody targeting the CD3 receptor on T lymphocytes, engineered to lack the Fc fragment. Its mechanism of action involves the induction of apoptosis in activated effector T cells, thereby modulating the autoimmune response and reducing the intensity of pancreatic β-cell destruction. At the same time, the drug promotes cytokine-mediated proliferation of regulatory T cells (Tregs), contributing to restoration of immune homeostasis [25]. A major advantage of Teplizumab is that it does not require long-term administration and does not induce chronic immunosuppression, setting it apart from conventional immunomodulatory therapies. In 2022, the U.S. Food and Drug Administration (FDA) approved Teplizumab for delaying the onset of clinical T1D in individuals aged 8 years and older with stage 2 (preclinical) disease markers. The therapeutic regimen consists of a 14-day course, which has been shown to delay progression to insulin dependence by 2–4 years. In some clinical reports, disease onset was delayed by up to 11 years, although efficacy is closely correlated with the disease stage at initiation and the preserved functional β-cell mass.

This drug can also be used to enhance β-cell viability in individuals with early clinical-stage T1D. Clinical trial data indicate that two 12-day courses of Teplizumab administered to patients with newly diagnosed T1D (within 6 weeks of diagnosis) result in a significant increase in stimulated C-peptide levels by week 78 [42].

Key advantages of Teplizumab include its short treatment duration (12–14 days), in contrast to agents requiring continuous or repeated administration, and the absence of long-term immune suppression. Laboratory studies have shown that Teplizumab induces selective functional depletion of $CD8^+$ effector T lymphocytes targeting β-cell antigens, thereby reducing the intensity of autoimmune response [43]. Meanwhile, there is a rapid recovery of immunocompetent cell populations in peripheral blood without an associated increase in infectious complications. Reported adverse effects, such as transient lymphopenia, mild skin reactions, and headache (cephalalgia), are generally self-limiting and do not require additional medical intervention [44].

Cell therapy

Current research in T1D treatment is increasingly focused on islet cell (IC) transplantation strategies aimed at restoring physiological glycemic regulation and endogenous insulin secretion [45]. Despite its significant therapeutic potential, this approach faces major technological challenges, including the identification of an optimal source of insulin-producing cells (IPCs), ensuring their long-term viability, and preventing immune rejection.

In recent years, attention has shifted toward the use of stem cells (SCs), both allogeneic and autologous, due to the limited success of donor allogeneic or xenogeneic islet transplantation. The demonstrated oncological safety of alternative IPC sources has further accelerated the development of stem cell–based protocols.

Numerous experimental systems have been proposed to address key challenges such as maintaining cell survival, enhancing functional activity, and protecting the graft from immune-mediated aggression, which in T1D is intensified by the underlying autoimmune pro-

cess. Modern approaches employ genetic or physical protective mechanisms to eliminate the need for systemic immunosuppression, thereby minimizing complications.

The optimal implantation site remains under investigation, as no anatomical location has yet shown clear superiority. Current research efforts are particularly focused on approaches that demonstrate potential for medium-term clinical applicability.

Transplantation of insulin-producing cells derived from stem cells

A promising direction in cell therapy for T1D is the autotransplantation of insulin-producing islets derived from chemically induced pluripotent stem cells (CiPSCs). While the liver remains the conventional site for islet implantation, alternative implantation sites are being actively explored. A phase I clinical trial demonstrated the efficacy of islet transplantation under the rectus abdominis muscle in a patient with T1D [46]. This site allows improved monitoring of the graft and facilitates safe removal if necessary. Preclinical trials in primates confirmed the oncological safety of the cell line used. The patient received 1.5 million insulin-producing cells, generated using a modified pluripotent stem cell differentiation protocol [47]. Insulin independence was achieved 75 days post-transplantation and maintained throughout a 12-month follow-up. The patient remained in stable normoglycemia, with >98% time in range and glycated hemoglobin (HbA1c) around 5%.

It should be noted, however, that the patient was already on immunosuppressive therapy due to a previous liver transplant, which limits objective assessment of the transplant's immunogenicity. In theory, the use of autologous SCs minimizes rejection risk, though the possibility of recurrence of autoimmune destruction of β-cells cannot be ruled out. To obtain more definitive conclusions and assess potential long-term complications, data from larger patient cohorts with extended follow-up periods (≥5 years) are needed.

Other studies have also reported successful transplantation of islets differentiated *in vitro* from autologous SCs [48].

An alternative approach involves the use of donor embryonic stem cells differentiated into islet cells (ICs). Transplantation of such islets into the liver has shown promising efficacy [49]. However, achieving insulin independence still requires immunosuppressive therapy. Consequently, current research focuses on developing technologies that can provide sustained protection of the graft from autoimmune and alloimmune aggression without systemic immunosuppression.

Mechanical protection methods

Various encapsulation strategies have been explored to enhance the efficacy of IPCs transplantation [50]. These methods shield the graft from immune reactions while maintaining adequate metabolic exchange to sustain cell functionality. Promising results have been reported with alginate-based microcapsules coated with PMETAC polymer [51]. Coatings containing 0.4% PMETAC exhibit selective permeability, supporting cell viability and enhancing the functional activity of transplanted IPCs. The demonstrated stability, target selectivity, and low cytotoxicity of this system in both *in vitro* and *in vivo* models highlight its potential for further clinical development.

The Cell Pouch system (Sernova, Canada) has gained considerable recognition as an implantable device designed to provide a favorable microenvironment for the long-term and efficient function of insulin-producing cells (IPCs). The system consists of a biocompatible chamber made of non-resorbable polymer materials, shaped into cylindrical compartments. Following subcutaneous implantation, a well-vascularized biological niche forms within approximately 14 days, creating an optimal site for the localization of encapsulated pancreatic ICs.

Clinical results have demonstrated long-term cell survival, minimal adverse effects, normalization of HbA1c levels, and insulin independence lasting up to four years [52]. However, these outcomes were achieved under concurrent immunosuppressive therapy. To ensure reliable protection of IPCs from autoimmune destruction, conformal coating technology, which is currently undergoing clinical evaluation, has been proposed [53]. This approach employs a mechanically stable polymer hydrogel matrix that envelops the transplanted islets, providing selective permeability for biomolecules while preserving physiological hormone secretion kinetics. Preclinical trials have shown that such modified cell transplants, when implanted into pre-vascularized biocompatible chambers, achieve normal glycemic control and sustained insulin independence.

Genetic protection methods

Allogeneic stem cell therapy VX-880 (Vertex Pharmaceuticals, USA) has demonstrated high clinical efficacy. IPCs transplanted into the hepatic portal vein system show strong engraftment and significant functional activity by day 90 post-transplant. This therapy leads to reductions in HbA1c levels, insulin requirements, and episodes of severe hypoglycemia [54]. However, its widespread clinical use remains limited by the need for long-term immunosuppressive therapy. As a result, it is currently reserved for T1D patients who are resistant to standard treatment and experience frequent, uncontrolled hypoglycemia, where preventing life-threatening complications outweighs the risks associated with immunosuppression.

Clinical trials are underway for a new therapy, VX-264 (Vertex Pharmaceuticals, USA), a next-generation

therapy using encapsulated ICs that eliminates the need for systemic immunosuppression. In parallel, Vertex Pharmaceuticals and ViaCyte are advancing a CRISPR/Cas9 genome editing strategy [55], which has demonstrated preclinical safety. This approach involves genetically modifying IPCs to remove specific markers that typically trigger immune rejection, thereby enabling transplantation without immunosuppression.

Further innovations aim to enhance both safety and functional integration of genetically engineered cells by implanting them in optimized microenvironments [56]. A key example is VCTX210 therapy (CRISPR Therapeutics; ViaCyte, USA; Switzerland), based on implantation of differentiated pluripotent SCs into specialized implantation devices designed to promote vascular integration and support physiological metabolic function.

Another approach is being developed by Sana Biotechnology (USA), which employs allogeneic islet transplants derived from induced pluripotent SCs or donor tissue. These cell lines are genetically engineered using HIP (Hypoimmune Platform) technology, enabling immune evasion without the need for immunosuppressive therapy [57]. In a patient with T1D, intramuscular transplantation of donor hypoimmune islets showed strong survival and high functional activity of ICs over a 28-day follow-up period [58].

Controlled cell therapy

In cell-based therapies, evaluating treatment safety and efficacy is essential yet often challenging. Minutia (USA) is developing a stem cell replacement therapy that enables *in vivo* monitoring of transplanted cells. The forearm is proposed as the implantation site, while nanosensor technology is used to monitor cell status in real time [59]. These nanostructured biosensors, integrated into transplanted cells, can detect phenotypic changes and assess immune system activity. Continuous feedback on the performance of IPCs provides critical information for predicting transplant rejection and guiding subsequent treatment tactics.

Pancreatic tissue engineering

A key challenge in islet transplantation is the reduced lifespan and functional activity of ICs due to the loss of their extracellular matrix (ECM). The natural microenvironment of the pancreas not only provides structural support but also facilitates intercellular communication and interaction with cytokines. Reconstructing this microenvironment for ICs using various cell types and biomaterials enhances vascularization and oxygenation, promoting optimal cell adhesion and proliferation at the transplant site.

Recent advances in tissue engineering and 3D bioprinting have opened the possibility of creating pancreatic tissue-engineered constructs (TECs) that closely mimic the native architecture, composition, and functionality of the human pancreas [60]. Such constructs should integrate both non-cellular components (e.g., hydrogels, polymers) and cellular elements (e.g., IPCs and supporting cells) to ensure physiological insulin secretion and normoglycemia.

Active research focuses on developing decellularized matrices that replicate the spatial and biochemical characteristics of native pancreatic tissue [61, 62]. The major advantage of these matrices lies in their low immunogenicity, achieved through complete removal of cellular material during decellularization. This approach has shown promising results in preclinical trials, with ongoing efforts aimed at identifying optimal materials and transplantation sites.

For instance, intrasplenic implantation of pancreatic TECs composed of floating islet-like cultures and a biodegradable, collagen-containing matrix in rats demonstrated good morphological preservation and sustained functionality. However, its hypoglycemic effect was less pronounced compared to intraperitoneal transplantation of similar TECs [63]. Moreover, intraperitoneal transplantation of a bioartificial pancreas – constructed from a decellularized human pancreas combined with allogeneic islets – in a rat T1D model resulted in more stable and prolonged glycemic control than transplantation of isolated islets of Langerhans [64].

The integration of these tissue-engineered platforms with advanced immunomodulatory strategies holds the potential for achieving a qualitative breakthrough in T1D treatment. Nonetheless, successful clinical translation will require extensive multi-phase preclinical and clinical studies to confirm the long-term safety, biocompatibility, and functional efficacy of these technologies.

COMBINATION OF ISLET CELL TRANSPLANTATION AND IMMUNOTHERAPY

An effective strategy to overcome the limitations of systemic immunosuppression in cell therapy is the use of its selective alternative – immunotherapy. One of the most promising developments in this field is Tegoprubart (Eledon Pharmaceuticals, USA), a therapeutic agent whose mechanism of action is based on selective blockade of the CD40L ligand. This therapeutic strategy induces dysregulation of intercellular signaling interactions by inhibiting costimulatory signals critical for T-lymphocyte activation [65].

Unlike traditional immunosuppressive drugs, Tegoprubart avoids systemic toxicity while effectively preventing both acute and chronic graft rejection. Preliminary clinical data demonstrate its high therapeutic efficacy in the context of islet cell transplantation: treatment with Tegoprubart resulted in a 3–5-fold increase in graft survival compared to standard immunosuppression protocols. Patients achieved normoglycemia without

the use of exogenous insulin within 2–4 weeks after transplantation, accompanied by a 2.7–3% reduction in HbA1c levels [66].

These findings underscore the potential of targeted immunomodulation as a means to minimize the risks associated with long-term immunosuppression.

DISCUSSION

The advances summarized in this review highlight a range of innovative strategies offering promising prospects for the treatment of T1D. Given the complex and heterogeneous pathogenesis of this disease, as well as its variable clinical presentation, it remains impossible to establish a standard universal treatment protocol. Consequently, there is an increasing shift toward personalized therapeutic approaches, in which different modalities are tailored to the specific case to achieve optimal outcomes.

At present, insulin therapy remains the cornerstone and only widely implemented treatment for T1D. Despite its inherent limitations, this approach is likely to remain indispensable in clinical practice for a long time to come. However, continuous scientific progress and accumulated clinical experience are driving its evolution. Modern insulin formulations and delivery systems have greatly enhanced glycemic control and minimized interference with daily life activities.

Modern advances in immunotherapy are already being successfully applied in the treatment of the first patients and are gradually entering broader clinical practice. These approaches can delay the onset of T1D in individuals with preclinical disease and improve glycemic control in patients with preserved residual islet cell function. The scientific community has proposed distinct T1D endotypes, each characterized by specific etiological and pathogenic mechanisms. Selecting an appropriate immunotherapy mechanism based on these endotypes may significantly enhance treatment efficacy.

Meanwhile, progress in cell therapy offers new opportunities for patients with complete β-cell destruction and absolute insulin deficiency. In such cases, technologies ensuring robust protection of transplanted cells from immune attack become crucial. Among emerging strategies, the combination of islet cell transplantation and targeted immunotherapy appears particularly promising, as it enables selective modulation of immune pathways while improving overall therapeutic effectiveness.

CONCLUSION

T1D remains a major challenge for modern medicine. Despite significant progress in existing treatment methods, adequate disease control is still difficult to achieve in most patients. However, emerging modern approaches, developed and refined over many years, are now approaching widespread clinical application. Several of these innovations are in the final stages of clinical trials, while others have already received approval for clinical use.

The variety of available solutions helps address the specific limitations of individual therapeutic modalities. The high level of modern science, combined with a personalized approach to treatment, offers strong prospects for a substantial improvement in the overall quality of life of patients living with T1D.

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