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REVIEW

Latest advancements in the development of new therapies for type 1 diabetes

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ABSTRACT
This study aims to explore new treatments for type 1 diabetes that could serve as an alternative or adjunct to insulin therapy. This is a literature review based on a search of relevant scientific articles in PubMed, Scopus, Google Scholar, and Cochrane Library databases. The scrutiny of publications revealed that the introduction of glucagon-like peptide-1 agonists into insulin therapy can improve disease control and reduce the frequency of hypoglycaemic episodes. While immune therapy is pathogenetically justified, its utility is limited in patients with recent onset of type 1 diabetes. It may, however, find application in prophylaxis in individuals at increased risk of developing this type of diabetes. Concurrently, stem cell therapy is under active investigation in clinical trials and has shown promise in reducing insulin dependence, improving β-cell function and controlling glucose levels. In addition, stem cells have demonstrated efficacy in treating complications of diabetes such as diabetic nephropathy, peripheral neuropathy and diabetic angiopathy. There is compelling evidence supporting the significant potential of gene-editing technology. Intravenous administration of T-regulatory cells, as one method of cell therapy, shows potential in stabilising the course of diabetes and slowing its progression. However, further research is warranted to confirm efficacy. While gene therapy holds promise, much of its research is currently in the preclinical stage. Further development of innovative therapies for type 1 diabetes has the potential to enhance the quality of life of patients, improve disease control and prevent the development of complications *(Fig. 1, Ref. 54)*. Text in PDF www.elis.sk
KEY WORDS: diabetes type 1, treatment, cell therapy, insulin, pancreatic β-cells.

Introduction

Type 1 diabetes mellitus is an autoimmune disease, characterized by the destruction of β-cells of pancreatic Langerhans islets. This process leads to absolute insulin deficiency and subsequent disorders of carbohydrate metabolism. Contrary to wide-spread beliefs, recent scientific data challenge the notion that type 1 diabetes exclusively affects young people. According to a study by N.J. Thomas et al, more than 40% of cases of type 1 diabetes mellitus develop in individuals aged 30 to 60 years, which is explained by genetic predisposition to the development of the disease (1).

The need to search for modern approaches to the treatment of type 1 diabetes is primarily caused by the high prevalence of this pathology. Over the past few years, the frequency of this type of diabetes worldwide has increased from 2% to 5% (2). In Kazakhstan, similar trends are noted. Due to the introduction of the Unified Health Information System, it has become possible to conduct large-scale epidemiological studies. According to the data published by Galiyeva et al, the periodic prevalence rate of type 1 diabetes mellitus in juvenile patients increased from 48.8 to 179.1 during the period from 2014 to 2021 (3). Concurrently, the mortality rate attributable to this nosologic entity in children also increased from 0.18 to 0.67 over the same timeframe. Likewise, in the adult population, the incidence of type 1 diabetes per 1000 people rose from 86 cases in 2014 to 152 cases in 2019 (4).

The main consequences of insufficient compensation for diabetes mellitus are the development of complications, early disability of patients, significant deterioration of the quality of life and reduction in life expectancy. According to Bazarbekova et al, an adequately compensated course of the disease is achieved solely in 21% of patients (5). In some cohorts of patients, decompensation of the disease can be extremely pronounced. Thus, according to the results of the analysis of case histories of inpatients in the Diabetes Centre of the Internal Medicine Clinic of Asfendiyarov Kazakh National Medical University, it was found that the level of glycosylated haemoglobin in patients with grade 1 diabetes mellitus averaged 10.01±0.2%, which is significantly higher than the recommended value of 7% (6). The high prevalence of decompensated diabetes mellitus leads to a high prevalence of complications (7, 8).

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The complexity of treating type 1 diabetes is attributed to imperfections of existing therapies (9). Currently, the common approach is to combine short-acting and long-acting insulin preparations, emulating the natural pattern of basal and postalimentary levels of insulinemia (10). Nevertheless, differences in pharmacokinetics between endogenous insulin and insulin preparations often hinder achieving a balance between glycaemic and insulinemic levels in the patient. Thus, the period of circulation of preparations in the blood not only is short but also falls short of the duration of postprandial hyperinsulinemia. The effect of prolonged insulin, which is administered once a day, slightly exceeds 24 hours, leading to daily variability of insulin concentration in the blood of patients (11). Although the utility of insulin pumps surpasses the basal-bolus regimen of insulin therapy in terms of relative dosing accuracy and greater convenience, it still falls short of achieving complete control of the disease (12, 13). Thus, the search for high-tech methods of diabetes mellitus treatment is in high demand.

The study aims to explore current developments in innovative treatments for type 1 diabetes.

Materials and methods

Studies published over a 20-year period (from 2003 to August 2023) were analysed. A literature search was conducted in scientometric databases, including the PubMed search engine created by the National Centre for Biotechnology Information, the SCOPUS database of Elsevier academic publishing house, the Google Scholar search engine, and the Cochrane Library database of systematic reviews of randomised clinical trials. The primary retrieval of literature data relied on keywords: "diabetes mellitus", "type 1 diabetes", "insulin deficiency", "endocrinological pathology", "β-cell deficiency" "gene therapy", "cell therapy", "stem cells", "new approaches", "treatment perspectives", "new methods", and "innovations". The literature search was conducted in Russian, English and Kazakh, with these terms translated into the respective languages for use in the search.

The criteria for selecting publications for primary data retrieval were based on accessibility to the full text of articles in the public domain, possibility to get access through scientific library resources, as well as the language of articles (English, Russian or Kazakh). The inclusion criteria encompassed literature reviews (systematic and non-systematic) and meta-analyses as well as clinical trials. Exclusion criteria comprised inability to evaluate the full text of the article, publications focused on the description of a single or serial clinical case, expert opinions lacking statistical support, promotional articles commissioned by pharmaceutical companies, the presence of a conflict of interest among the authors, popular science articles in the mass media, and publications based on the results of studies conducted on cell cultures or animals.

Publications describing studies on animals or cellular models were included solely when they met the condition of being focused on n the prospects of using gene therapy in the treatment of type 1 diabetes. While clinical trials in this area have not been conducted yet, notable progress has been achieved in preclinical studies. Consequently, the study authors have chosen to highlight gene therapy in this literature review. The authors independently selected publications for further analysis. Subsequently, as a result of subsequent discussion, 93 scientific articles were selected for further analysis. Randomised clinical trials and systematic literature reviews with meta-analyses were approved for further analysis without an exhaustive review of the materials and methods section, given that the methodology of these studies aligns closely to the "gold standard" among scientific publications.

For non-systematic literature reviews and clinical trials conducted without randomisation, individual assessment of each publication was required for inclusion in this literature review. The study authors carefully analysed the materials and methods section of the publications. The publications identified as having substantial methodological flaws significantly increasing the risk of drawing erroneous conclusions due to a high probability of cognitive distortions and possible bias of the authors, were excluded from further analysis. Non-systematic literature reviews represented the most diverse group of publications. Given the absence of standardised methods for assessing the quality of non-systematic literature reviews, this study did not consider publications in journals with a low impact factor. However, studies from highly authoritative sources were still taken into account.

In total, 36 scientific publications were analysed. Due to their heterogeneity, particularly the differences in study endpoints and approaches to patient follow-up, a meta-analysis of studies was not performed.

Results and discussion

Since the discovery of insulin in 1922, its use has been continually refined. Recent advances in insulin therapy are described in the literature review by Cheng et al (14). The development of ultrashort-acting forms of insulin has been focused on a more rapid onset of action of the drug to avoid postprandial hyperglycaemia and its undesirable side effects. Fiasp ultrashort insulin was approved by the FDA in 2017 and Afrezza inhaled insulin has been approved since 2014. Other drugs are undergoing clinical trials. The ultralong-acting forms of insulin, insulin glargine U-300 and insulin degludec, were approved by the FDA in 2015, with a duration of effect of 30 and 42 hours, respectively. To avoid the disadvantages associated with injectable administration, oral insulin is under development.

The widespread introduction of continuous glycaemic monitoring devices has made it possible to create an "artificial pancreas", a system comprised of a sensor component that detects blood glucose levels and an effector component that delivers insulin to the body (usually an insulin pump). The software of this device makes it possible to identify the patient's need for insulin at particular timepoints based on glycaemic parameters. In the future, it is anticipated that software development will allow for predicting the dynamics of glycaemia depending on factors such as time of day or activity load in individual patients. Consequently, this will facilitate the determination of the patient's insulin requirements.

While such devices have already been introduced into practice, further refinement is needed (15).

Glucagon-like peptide-1 (GLP-1) agonists have been successfully used for several years in the treatment of type 2 diabetes mellitus, especially in patients with concomitant obesity. However, given the recent literature data, it is highly likely that GLP-1 agonists will be soon incorporated into the treatment of type 1 diabetes as well. A systematic literature review with meta-analysis was published in 2020 by Dimitrios et al (16). Based on the results of the evaluation of 5 randomised clinical trials with a total number of 2,445 participants, it was found that the use of liraglutide in addition to standard insulin therapy helps improve glycaemic control, reduces the need for insulin preparations, and lowers the frequency of hypoglycaemic episodes.

In 2021, the results of randomised clinical trials published by Dejgaard et al showed that the efficacy of liraglutide does not vary depending on the degree of compensation of diabetes mellitus, body mass index and different regimens of insulin therapy (17). In 2021, von Herrath et al. published the results of their study, concluding that the combination with the interleukin 21 antagonist liraglutide is not less effective in preserving pancreatic β-cell function compared to liraglutide monotherapy. Moreover, it allows for a better safety profile of use (18).

Immunotherapy

Diabetes type 1 develops due to autoimmune destruction of pancreatic β-cells. The autoimmune origin of the disease sets the stage for the development of immune therapy. Atkinson et al describe the pathogenesis of type 1 diabetes as follows: excessive activation of T-helper cells overstimulates B-lymphocytes, which in turn, leads to the production of autoantibodies, and activation of cytotoxic T-lymphocytes and NK-cells, macrophages, dendritic and antigen-presenting cells (19). A potential disadvantage of immune therapy, according to von Scholten et al, is the fact that the prospects for its use are limited to patients with recent manifestations of diabetes mellitus, as well as healthy individuals at high risk of developing diabetes (20). Thus, for the full application of immunotherapy in clinical medicine, it is urgent to search for biomarkers that can be used to predict the progress of diabetes mellitus or its diagnosis at an early stage.

According to the findings of the literature review by Zhang et al, zinc transporter protein 8 (ZnT8) holds significant importance. ZnT8-specific CD8+ T-lymphocytes are prevalent in most patients with type 1 diabetes and play a key role in disease progression (21). Therefore, the use of ZnT8 as a target of immunotherapy to improve beta-cell function may be promising, although current studies are still in the theoretical stage. One domain of immunotherapy is represented by an approach aimed at reducing the severity of overall inflammation. Although some drugs have not lived up to the expectations, there have been promising results in studies of others. For example, in a double-blind, placebo-controlled study, tocilizumab (a monoclonal antibody to interleukin 6 receptors) did not result in the preservation of pancreatic β-cell function (22). However, the drug golimumab (monoclonal antibody to tumour necrosis factor α receptors) was extremely effective in increasing insulin production by pancreatic β-cells in patients aged 6 to 21 years with recent onset of type 1 diabetes (23).

Despite the prospects for the development of immunotherapy in the treatment of type 1 diabetes mellitus, several authors suggest that immunotherapy alone may not be sufficient to achieve remission. B.O. Roep et al. emphasise the need to combine immunotherapy with cell therapy in patients with type 1 diabetes mellitus to achieve a persistent clinical effect (24). The term “cell therapy” combines strategies based on the use of stem cells and the use of polyclonal regulatory T cells (Tregs).

Stem cell therapy

The experience of pancreatic cell transplantation served as a prototype for the development of stem cell therapy. In 2000, Shapiro et al published a report on a series of clinical cases with a one-year follow-up. Seven patients with severe type 1 diabetes mellitus underwent transplantation of pancreatic islets from deceased donors (25). This method of treatment is known as the Edmonton Protocol. Although this approach has been a breakthrough in the treatment of particularly severe cases of type 1 diabetes, especially in those with frequent hypoglycaemia, its permanent use is limited, primarily due to the shortage of material for transplantation, and need for constant immunosuppression in recipients, which increases the risk of systemic infections and malignancies. The prerequisite for the development of stem cell therapy was the understanding of the key properties of stem cells. Unlike other cells, stem cells have a unique ability to proliferate and differentiate, which positions them as precursors to virtually any cell in the human body and allows them to undergo an unlimited number of divisions. Another peculiarity of stem cells lies in their uneven division. In this process, one of the two daughter cells differentiates while the other retains its stem cell status, providing the potential for further tissue regeneration. Finally, the “homing” effect should be noted, owing to which stem cells can migrate to the target tissue and potentially replace its lost function (26).

Different protocols for β-cell creation are based on a common principle that pluripotent stem cells are exposed to pancreatic developmental transcription factors (such as fibroblast growth factor, bone morphogenetic protein and activin A). According to the data from Murry and Keller, the most effective approach to generate certain highly differentiated cells from stem cells is to recreate embryonic development (27). Most protocols typically involve five to seven steps with duration ranging from 20 to 30 days in total. Once the differentiation process is completed, β-cells retain their identity throughout the further cultivation period (28). Several types of stem cells are used in cell therapy research, particularly haematopoietic, induced pluripotent and mesenchymal stem cells (MSCs). Currently, mesenchymal stem cells are the most commonly studied in clinical trials. They are relatively easy to isolate, exhibit low immunogenicity, are comparatively affordable, and their use does not pose ethical concerns. The results of preclinical studies also indicate the effectiveness of mesenchymal stem cells as immunomodulators (29).

In 2022, the results of a triple-blind randomised placebo-controlled study focused on the administration of mesenchymal

stem cells were published (30). The study included 21 patients aged 8 to 40 years. All patients were diagnosed with type 1 diabetes mellitus at least 6 weeks before being included in the study. Inclusion criteria for the study required a fasting C-peptide level of at least 0.3 nmol/L and the presence of at least one of three types of autoantibodies to pancreatic β-cells in serum. Stem cells were obtained from the bone marrow of 11 patients included in the main group. The transplantation was performed by intravenous infusion of the drug lasting over 30–40 minutes. Ten patients received a placebo. Participants were monitored for one year. No transplant side effects were observed in either group. However, glycated haemoglobin levels were significantly lower in the intervention group compared to the placebo group, and C-peptide levels were higher. After the transplantation, anti-inflammatory patterns were observed in the serum of patients in contrast to the predominance of proinflammatory cytokines. Moreover, the quality of life of these patients improved significantly.

The results of an open-label clinical trial, in which pancreatic endodermal stem cells were implanted subcutaneously in 15 patients as part of an encapsulated vascularised device were published in 2021 (31). All patients received immunosuppressive therapy to avoid implant rejection. The results of the study showed a statistically significant increase in fasting C-peptide levels in the patient's blood compared to those observed prior to the study. In addition, C-peptide levels were found to increase in response to glucose administration or food intake, followed by a decrease. This study marks the first confirmation of the potential treatment of type 1 diabetes by transplanting stem cells that secrete insulin postprandially. The duration of the effect of stem cell transplantation was investigated in a non-randomised prospective study by Gu et al (32). This study was focused on the use of autologous haematopoietic stem cells in adolescents with recent onset of type 1 diabetes. Twenty study participants received classical therapy with insulin preparations, the other 20 underwent transplantation and continued to use insulin as needed according to their glycaemic levels. Two years after stem cell transplantation, 14 patients in the main group stopped using insulin, of whom 3 individuals remained insulin-free after 4 years owing to normal glycaemic levels. However, the other 11 subjects had to resume insulin injections. Nevertheless, 4 years after transplantation, the difference in daily insulin doses between the groups remained statistically significant (0.49±0.32 U/kg/day vs 0.79±0.18 U/kg/day, respectively, $p<0.01$).

Confirmation of the immunomodulatory properties of stem cells was obtained in the study of Ye et al (33). The study included patients aged 12 to 35 years with newly diagnosed type 1 diabetes mellitus (at least 6 months before the study). One year after autotransplantation of haematopoietic stem cells, the study participants showed a statistically significant decrease in the level of T-helper types 1 and 17, interleukins 2 and 17, γ-interferon, along with an increase in the concentration of transforming growth factor β which was not observed in the group of patients receiving insulin. Several systematic literature reviews with meta-analyses support the conclusions of the publications analysed above (34, 35). Stem cells are a safe method of therapy in type 1 diabetes mellitus, capable of enhancing glycaemic control and improving the function of pancreatic β-cells, thereby affecting the reduction of insulin dose. However, as noted by Madani et al, further randomised clinical trials are needed for a more comprehensive assessment of the effect of stem cell therapy on the course and prognosis of diabetes mellitus (36).

Data supporting the effectiveness of stem cells for the prevention of the development of chronic complications of type 1 diabetes mellitus were published in a 2020 article by Wu et al (37). Eight years after undergoing stem cell transplantation, the patients were significantly less likely to develop complications such as peripheral neuropathy and diabetic nephropathy compared to the control group. This study utilized a combination of autotransplantation of bone marrow-derived mononuclear stem cells and allotransplantation of cord blood mesenchymal cells. Additionally, a meta-analysis by Y. Sun et al. demonstrated the efficacy of stem cell therapy in the treatment of diabetic foot (38). Patients subjected to stem cell therapy experienced less pain at rest and during walking, faster healing of lesions (ulcers and wounds), and a lower rate of amputations compared to those who received only traditional conservative treatment.

Treatment aimed at normalising the function of regulatory T cells (Tregs) is known as T-regulatory therapy. This method is a combination of immune and cell therapy. In 2022, the results of the first double-blind placebo-controlled study investigating this therapy method were published (39). The study involved a subcutaneous injection of a preparation consisting of 6 β-cell peptides. The study included patients with the HLA-DRB1*0401 genotype who had experienced the debut of diabetes mellitus at least 4 years prior to their inclusion in the study. During the 24-week study period, C-peptide levels in the blood of patients who received placebo decreased significantly. In contrast, in the group of patients receiving active treatment, C-peptide levels remained at the same level in half of the patients. It was concluded that Tregs therapy may slow the progression of diabetes. In addition, the authors of the paper noted an increase in the expression of T-regulatory cells when the experimental drug was administered. Although no statistically significant changes were found in daily insulin dosage and glycosylated haemoglobin levels between the groups, the authors plan to continue research in this direction.

According to some data, combining Tregs therapy with low-dose interleukin 2 (IL-2) may be effective. Infusion of polyclonal T-regulatory lymphocytes is a safe method of maintaining immunological tolerance in patients with type 1 diabetes mellitus, but the effect of such therapy is limited by a short duration of action. Already 90 days after a single injection of drugs, less than 25% of the active substance was found in the blood of recipients. S. Dong et al. suggested that the combination of Tregs with IL-2 could extend the therapeutic effect (40). The number of injected and endogenous T-regulatory lymphocytes indeed increased after the experimental therapy. However, their decrease was accompanied by a rise in the number of natural killer cells, MAIT-cells and CD8 T-helper cells. Thus, the combined use of Tregs and IL-2 in patients with type 1 diabetes cannot be recommended as it leads to even greater hyperactivation of the immune system.

Gene editing

A separate role in advancing the latest therapies for type 1 diabetes is attributed to the development of gene editing technologies. These methods enable modifications in DNA by cutting out or replacing genes associated with a particular pathology.

There are several types of gene editing technologies, including CRISPR-Cas9, TALENs, and ZFNs (41). In 2021, Baraja et al published an article reviewing the successful application of CRISPR-Cas9 technology in mice across several varied experiments (41). The study revealed that the deletion of the RNLS gene associated with type 1 diabetes renders β-cells resistant to autoimmune damage, thereby preserving pancreatic function.

Even more promising is the synergy of gene editing technologies and stem cell therapy. In 2020, Lim et al reported successful results in creating a line of pancreatic β-cells that produce interleukin 10 (42). Interleukin 10, an anti-inflammatory cytokine, has been shown to reduce autoimmune damage to β-cells and enhance the resilience of stem cells as part of the immune system of recipients after transplantation. Additionally, in 2021, Alzhanuly et al demonstrated the application of CRISPR-Cas9 technology in human cells to modulate insulin production (43).

Pharmaceutical companies are also engaged in the development of genetically modified stem cells. Particularly, in March 2023, Vertex Pharmaceuticals Incorporated and CRISPR Therapeutics announced the start of the joint development of insulin-producing stem cells that would be hyperimmune and would not require the use of immunosuppressive therapy in recipients. This would avoid the side effects of cytostatic therapy and improve the safety of using stem cells in diabetic patients (44).

Results of the application of TALENs and ZFNs technologies in the development of treatments for type 1 diabetes mellitus have not been published so far.

Gene therapy

The term "gene therapy" refers to inducing changes in the genetic material within a cell. This approach may involve the intracellular introduction of new genes, replacing defective genes with functional ones, or switching off defective disease-causing genes. Type 1 diabetes mellitus is a multifactorial disease that develops as a result of the interaction of genetic predisposition and environmental factors. Research, including a full genome-wide association search (GWAS), has identified more than 60 genes associated with the development of type 1 diabetes mellitus by 2013 (Fig. 1). The development of gene therapy may provide a more holistic approach to treatment and, in some cases, possibly allow for a complete cure of the disease.

Unfortunately, the use of gene therapy is associated with several difficulties, primarily due to the peculiarities of the delivery of genetic material inside the cell. As a rule, viral vectors are used to transport genetic material or proteins inside the cell, although non-viral methods are also being developed. The most commonly used currently are adenovirus, adeno-associated virus type 8, retrovirus, and lentivirus. Although viral vectors are devoid of pathogenicity factors, in the case of type 1 diabetes, given the compromised immune system of patients, the effects of viral vectors may provoke an immune response and/or worsen the course of diabetes. Plasmids are non-viral methods of delivering genetic information into the cell (46).

The current landscape of gene therapy research is conducted on animals. Therefore, the safety of using this method in humans has yet to be assessed. In addition, ethical disputes, and social ambivalence towards gene therapy impede the progress in research. There are several primary directions that shape the trajectory of gene therapy advancement. One approach involves activation of gene expression (gene overexpression). It is recognized that type 1 diabetes develops with insufficient expression of some genes, par-

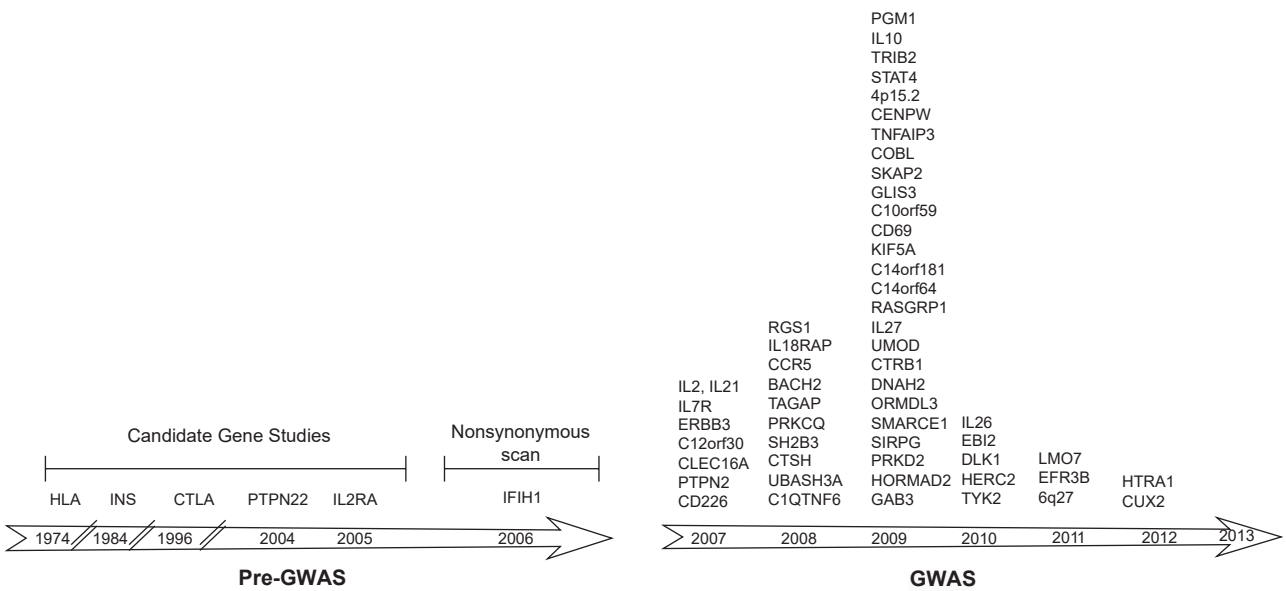

Fig. 1. Chronology of the study of genes associated with the development of type 1 diabetes mellitus Source (45).

ticularly in genes of insulin-like growth factor 1, Reg3g protein, hepatocyte growth factor, and Klotho, a gene associated with increased longevity and regulation of various functions, including the sensitivity of receptors to insulin. Studies on laboratory animals provided compelling evidence that stimulating the expression of these genes can improve the course of type 1 diabetes (46–48).

Another avenue in gene therapy explores the use of viruses to deliver various proteins inside the cell. Noteworthy among these proteins are neurogenin-3 and beta-cellulin, which stimulate the formation of Langerhans islets in the pancreas and the subsequent synthesis of insulin by the β-cells (49). The pancreatic and duodenal homeobox 1 (PDX-1) protein, encoded by its eponymous gene holds significant importance as an activator of insulin, glucokinase, and somatostatin genes. While damage to the PDX-1 gene leads to the development of diabetes mellitus, attempts to deliver this protein intracellularly using an adenovirus vector have resulted in the development of severe hepatitis, precluding its further application (50). Positive outcomes have been reported with the use of α-1-antitrypsin, glucokinase, and leptin (51, 52).

Another viable strategy in gene therapy involves transplantation of cells expressing antidiabetic genes. In murine studies, this form of transplantation demonstrated a reduction in blood glucose levels and decrease in the concentration of autoantibodies to insulin in the blood (46). The utility of this approach *in vivo* is constrained by the necessity of future immunosuppressive therapy and intraoperative risks. Genetic vaccination also emerges as a possible way of both treating and preventing type 1 diabetes. DNA vaccination involves the introduction of plasmid DNA encoding an antigen into a cell, leading to suppression of the T-lymphocyte-mediated immune response to that antigen. However, this approach is relatively nascent, and needs further refinement and development (53).

In 2021, an article on the treatment of diabetic peripheral neuropathy with gene therapy was published (54). This clinical, randomised placebo-controlled trial marked advancement as the first of its kind, using gene therapy in diabetic patients. The study included 500 participants, comprising 336 subjects in the main group, and 164 in the control group. Patients in the main group received VM202, a plasmid containing hepatocyte growth factor DNA. J.A. Kessler et al. reported positive outcomes from this innovative therapy, noting a significant reduction in pain sensations among patients in the main group. The effect was even more pronounced in those who did not receive traditional symptomatic therapy (in particular, gabapentin or pregabalin).

In summary, the current state of gene therapy underscores the need of further development at a fundamental level (55). While positive strides have been made, it is premature to consider its widespread implementation in clinical practice.

Conclusions

The limitations associated with insulin therapy have propelled the development of innovative treatments for type 1 diabetes. This literature review scrutinised several key therapeutic domains, encompassing immune, cellular, and gene-based approaches, while also highlighting major innovations in injection therapy. Recent advances in insulin therapy involve the emergence of so-called closed-loop systems which simultaneously monitors glucose levels and delivers insulin. These systems are already available, but their excessive cost and innovative nature hinder their widespread introduction into practical healthcare.

GLP-1 agonists have shown promise as adjuncts to insulin therapy for patients with type 1 diabetes as shown in clinical studies demonstrating their beneficial effects on the disease course, including lower glycosylated haemoglobin levels, reduced frequency of hypoglycaemic episodes and reduced need for insulin. These drugs, which are widely used in endocrinology for the treatment of type 2 diabetes and obesity, can be successfully introduced into the treatment of type 1 diabetes. Stem cell therapy aims to correct the pathological loss of β-cells and restore their function. The main clinical trials are conducted in the context of autotransplantation of stem cells derived from the patient's bone marrow, followed by intravenous administration. This method has no side effects apart from those associated with immunosuppressive therapy and shows good results in restoring β-cell function and reducing the need for exogenous insulin.

Gene therapy remains under fundamental investigation. The intricacies of genes associated with the development of type 1 diabetes present challenges in deciphering effective therapeutic approaches. Notably, the sole clinical trial of gene therapy in diabetology focuses on peripheral neuropathy and needs to be confirmed by other studies. It is worth noting that patients with type 1 diabetes represent a diverse group with different clinical manifestations and pathophysiological features. This heterogeneity underscores the need for a personalised treatment approach, considering both phenotypic and genotypic differences in patients. Thus, further research in the management of type 1 diabetes should adopt multidirectional approach, acknowledging the diversity within this pathology and striving to identify optimal treatments for each category of patients.

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