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Gene therapy for diabetes mellitus: Current strategies, advances, and future perspectives

Subhadeep Ghosh[1], Ankita Panda[2], Payel Roy[3], Souvik Tewari[4*]
[1] Consultant Physician & Intensivist, Sanjeevani Polyclinic & Hospital, Midwest Hospital Asansol, West Bengal, India
[2] Guest Faculty, Department of Nutrition, Egra Sarada Shashi Bhusan College, West Bengal, India
[3] Department of Food Processing and Nutrition Science, IIEST, Shibpur, Howrah, West Bengal, India.
[4] Assistant Professor, Department of Food and Nutrition, Swami Vivekananda University, Barrackpore, West Bengal, India
Corresponding Author: Souvik Tewari

Abstract
Diabetes mellitus (DM) is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The global prevalence of diabetes has increased dramatically over the past few decades, posing a significant public health challenge. Conventional treatments, including insulin therapy and oral hypoglycemic agents, effectively manage blood glucose levels but do not cure the disease or prevent its long-term progression. Gene therapy has emerged as a promising therapeutic approach that aims to address the underlying molecular defects responsible for diabetes. By delivering, modifying, or regulating specific genes, gene therapy offers the potential for long-term glycemic control and even disease reversal. This article provides an overview of diabetes mellitus, the principles of gene therapy, current strategies, recent advances, challenges, and future prospects.

Keywords: Diabetes mellitus, gene therapy, insulin, beta-cell regeneration, gene editing, CRISPR-Cas9, stem cell therapy, viral vectors, non-viral vectors, precision medicine, hyperglycemia, type 1 diabetes, type 2 diabetes, personalized medicine

Introduction

Diabetes mellitus is one of the most prevalent non-communicable diseases worldwide (Budreviciute *et al*., 2020) [6]. According to the International Diabetes Federation (IDF), hundreds of millions of people are living with diabetes, and the number continues to rise due to aging populations, urbanization, obesity, and sedentary lifestyles (Saeedi *et al*., 2019) [27]. Diabetes significantly increases the risk of cardiovascular disease, kidney failure, neuropathy, retinopathy, and premature mortality (Deshpande *et al*., 2008) [8].

Current treatment strategies primarily focus on maintaining blood glucose levels within normal limits through insulin administration, oral antidiabetic drugs, dietary modifications, and lifestyle changes (Aloke *et al*., 2022) [3]. While these therapies improve quality of life, they require lifelong adherence and often fail to prevent progressive β-cell dysfunction (Sambhav *et al*., 2026) [28]. Consequently, researchers are investigating innovative approaches such as gene therapy that target the molecular mechanisms responsible for diabetes.

Diabetes Mellitus

Diabetes mellitus is a group of metabolic disorders characterized by chronic hyperglycemia due to impaired insulin secretion, insulin resistance, or both (American Diabetes Association, 2010) [4].

1. Types of Diabetes

1.1 Type 1 Diabetes Mellitus (T1DM)

Type 1 diabetes is an autoimmune disease in which pancreatic β-cells are destroyed by the immune system, leading to absolute insulin deficiency. Patients require lifelong insulin replacement therapy (Warshauer *et al*., 2020) [31].

1.2 Type 2 Diabetes Mellitus (T2DM)

Type 2 diabetes accounts for approximately 90–95% of diabetes cases. It is characterized by insulin resistance combined with progressive β-cell dysfunction. Major risk factors include obesity, sedentary lifestyle, aging, and genetic predisposition (Davies *et al*., 2026) [7].

1.3 Gestational Diabetes Mellitus (GDM)

Gestational diabetes develops during pregnancy and usually resolves after delivery. However, affected women have an increased risk of developing Type 2 diabetes later in life (Xie *et al*., 2026) [35].

1.4 Other Specific Types of Diabetes Mellitus

In addition to Type 1 diabetes mellitus, Type 2 diabetes mellitus, and gestational diabetes mellitus, there are several other specific types of diabetes that result from identifiable causes affecting insulin secretion or action (Jacobsen and Schatz, 2026) [15]. These forms are relatively uncommon but are clinically important because their diagnosis and management differ from those of the more common types of diabetes (Davies *et al*., 2026) [7]. They may arise from genetic mutations that impair pancreatic β-cell function or insulin action, such as maturity-onset diabetes of the young (MODY) and neonatal diabetes (Zagaroli *et al*., 2026) [37]. Diabetes can also develop secondary to pancreatic diseases, including chronic pancreatitis, pancreatic cancer, cystic fibrosis, or surgical removal of the pancreas, all of which damage insulin-producing β-cells (Bryliński *et al*., 2026) [5]. Certain endocrine disorders, such as Cushing's syndrome, acromegaly, hyperthyroidism, pheochromocytoma, and glucagonoma, can increase blood glucose levels by producing excess hormones that counteract insulin action. In addition, prolonged use of certain medications, including glucocorticoids (corticosteroids), thiazide diuretics, atypical antipsychotics, immunosuppressive agents, and some

antiretroviral drugs, may lead to drug-induced diabetes by causing insulin resistance or reducing insulin secretion. Diabetes may also occur following infections, particularly congenital viral infections such as congenital rubella and cytomegalovirus (CMV), which can damage pancreatic β-cells or trigger autoimmune responses. Identifying these specific causes is essential for selecting appropriate treatment strategies, managing the underlying condition, and improving long-term patient outcomes (Resmini *et al*., 2009) [25].

2. Pathophysiology of Diabetes

The pathophysiology of diabetes mellitus involves disturbances in the regulation of glucose metabolism resulting from impaired insulin secretion, insulin resistance, or a combination of both. Under normal physiological conditions, glucose homeostasis is maintained through the coordinated action of insulin, a hormone produced by the pancreatic β-cells of the islets of Langerhans. Insulin facilitates the uptake of glucose by peripheral tissues such as skeletal muscle and adipose tissue while suppressing hepatic glucose production, thereby maintaining blood glucose levels within a narrow physiological range. In Type 1 diabetes mellitus (T1DM), autoimmune destruction of pancreatic β-cells leads to an absolute deficiency of insulin, resulting in uncontrolled hyperglycemia and dependence on lifelong insulin replacement therapy. In Type 2 diabetes mellitus (T2DM), the primary abnormality is insulin resistance, in which peripheral tissues become less responsive to insulin (Fuentes-Barría *et al*., 2026) [10]. To compensate, pancreatic β-cells initially increase insulin secretion, leading to hyperinsulinemia. However, prolonged metabolic stress, glucotoxicity, lipotoxicity, oxidative stress, and chronic inflammation gradually impair β-cell function, resulting in β-cell exhaustion and inadequate insulin production. Persistent hyperglycemia further exacerbates cellular damage by promoting the formation of advanced glycation end products (AGEs), increasing oxidative stress, activating inflammatory pathways, and causing endothelial dysfunction (Lodi *et al*., 2026) [21]. These pathological processes contribute to the development of chronic diabetic complications, including cardiovascular disease, diabetic nephropathy, retinopathy, neuropathy, and impaired wound healing. Understanding the pathophysiology of diabetes is essential for developing targeted therapeutic approaches, including gene therapy, that aim to restore normal insulin secretion, improve insulin sensitivity, preserve β-cell function, and prevent disease progression (Suresh *et al*., 2026) [29].

Gene Therapy

Gene therapy is a therapeutic technique that involves introducing, removing, or modifying genetic material within a patient's cells to treat or prevent disease (Khan *et al*., 2026) [35].

Unlike conventional drug therapy, gene therapy seeks to correct the underlying genetic or molecular defects responsible for disease development (Ledri and Kokaia, 2026) [18].

3. Types of Gene Therapy

3.1 Somatic Gene Therapy

Somatic gene therapy is a form of gene therapy that involves introducing, modifying, or replacing genes in the somatic (body) cells of an individual to treat or prevent disease. Unlike germline gene therapy, the genetic changes made through somatic gene therapy are not passed on to future generations because they do not affect reproductive cells such as sperm or eggs. This approach is currently the most widely used and extensively studied in both preclinical and clinical research due to its relatively favorable safety and ethical profile. In the context of diabetes mellitus, somatic gene therapy aims to restore normal glucose regulation by delivering therapeutic genes to target tissues such as the pancreas, liver, skeletal muscle, or adipose tissue. These genes may promote insulin production, enhance insulin sensitivity, stimulate pancreatic β-cell regeneration, or protect β-cells from autoimmune destruction. Since the treatment is confined to the patient's body cells, any genetic modifications remain limited to the treated individual, making somatic gene therapy a promising and ethically acceptable strategy for developing long-term treatments for diabetes and other chronic diseases (Khan *et al*., 2026) [35].

3.2 Germline Gene Therapy

Germline gene therapy is a type of gene therapy in which genetic modifications are made to reproductive cells (sperm or eggs) or early-stage embryos (Pérez-Ballestero *et al*., 2026) [24]. Because these changes occur in the germ cells, the altered genetic material can be inherited by future generations, making the modifications permanent within a family lineage. The primary goal of germline gene therapy is to prevent the transmission of inherited genetic disorders by correcting disease-causing mutations before birth. Although this approach has the potential to eliminate certain hereditary diseases, it raises significant ethical, legal, and safety concerns, including the possibility of unintended genetic changes (off-target effects), unknown long-term consequences, and ethical issues related to altering the human genome (Mulvihill *et al*., 2017) [23]. Consequently, germline gene therapy is prohibited or strictly regulated in many countries and is not used in routine clinical practice. In the context of diabetes mellitus, germline gene therapy remains a theoretical approach and is not considered a practical or acceptable treatment option under current medical and regulatory standards (Wolf *et al*., 2019) [32].

3.3 Gene Delivery Systems

Gene delivery systems are essential components of gene therapy, as they are responsible for transporting therapeutic genes into target cells where they can be expressed to produce the desired therapeutic effect (Verma and Weitzman, 2005) [30]. The success of gene therapy largely depends on the efficiency, specificity, and safety of the gene delivery method. An ideal delivery system should protect the genetic material from degradation, accurately target the appropriate cells or tissues, achieve sufficient and sustained gene expression, and minimize immune responses or other adverse effects. Gene delivery systems are broadly classified into two categories: viral vectors and non-viral vectors. Viral vectors, such as adenoviruses, adeno-associated viruses (AAVs), retroviruses, and lentiviruses, are highly efficient at transferring genes into cells because they exploit the natural ability of viruses to infect host cells. In contrast, non-viral vectors—including liposomes, nanoparticles, polymers, and naked DNA—offer improved safety, lower immunogenicity, and easier large-scale production, although they generally exhibit lower gene transfer efficiency. The selection of an appropriate gene

delivery system depends on factors such as the target tissue, the size of the therapeutic gene, the required duration of gene expression, and the overall safety profile. In diabetes mellitus, efficient delivery of therapeutic genes to pancreatic β-cells, liver, skeletal muscle, or other metabolically active tissues is crucial for achieving sustained insulin production, improving insulin sensitivity, and preventing disease progression (Geng *et al*., 2025) [11].

Gene Therapy Strategies for Diabetes

Gene therapy for diabetes focuses on correcting the underlying molecular and cellular abnormalities responsible for the disease rather than simply managing blood glucose levels. The primary objectives of these strategies are to restore or enhance insulin production, improve insulin sensitivity in peripheral tissues, preserve or regenerate functional pancreatic β-cells, and prevent or reduce the autoimmune destruction of β-cells, particularly in Type 1 diabetes mellitus (Yan *et al*., 2024) [36]. Different therapeutic approaches involve delivering genes that encode insulin, growth factors, transcription factors, or immunoregulatory proteins to specific target tissues such as the pancreas, liver, skeletal muscle, or adipose tissue (Xie *et al*., 2025) [34]. Recent advances in gene editing technologies, including CRISPR-Cas9, and stem cell-based gene therapy have further expanded the potential for developing long-lasting or even curative treatments. Although many of these strategies are still under investigation in preclinical and clinical studies, they have demonstrated promising results in improving glucose homeostasis, reducing dependence on insulin therapy, and preventing the progression of diabetes. The major gene therapy strategies for diabetes include insulin gene therapy, β-cell regeneration, β-cell protection, immune modulation, enhancement of insulin sensitivity, and genome editing approaches, each targeting different aspects of diabetes pathogenesis (Addissouky, 2025) [17].

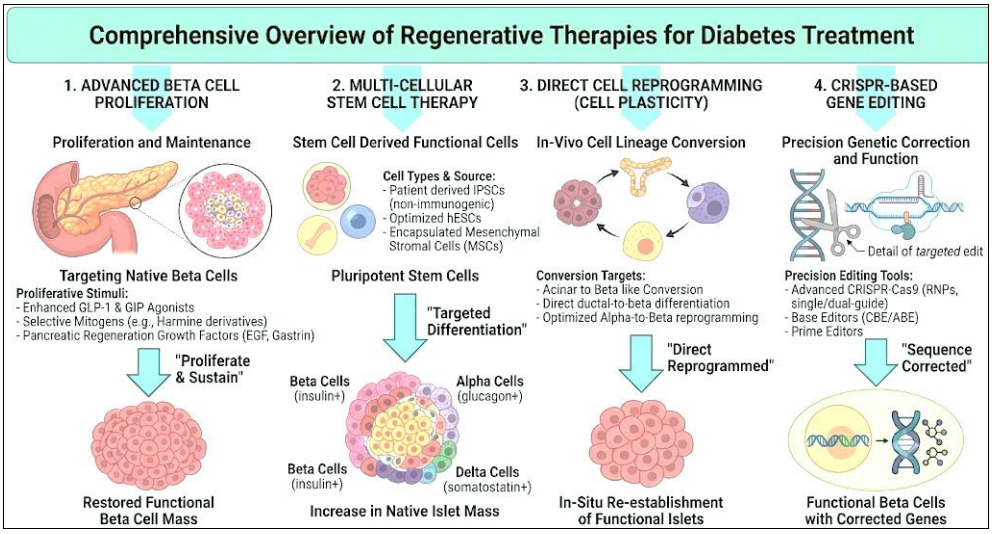

Fig 1: Comprehensive Overview of Regenerative and Gene Therapy Strategies for Diabetes Treatment, including Beta Cell Proliferation, Stem Cell Therapy, Reprogramming, and CRISPR-Based Gene Editing

1. Insulin Gene Therapy

Insulin gene therapy is one of the most extensively studied gene therapy strategies for the treatment of diabetes mellitus (Wong *et al*., 2010) [4]. This approach involves introducing a functional insulin gene into non-pancreatic cells, enabling them to synthesize and secrete insulin in response to elevated blood glucose levels. Since pancreatic β-cells are either destroyed in Type 1 diabetes or become dysfunctional in advanced Type 2 diabetes, alternative tissues such as liver cells (hepatocytes), skeletal muscle cells (myocytes), and intestinal cells are explored as potential targets for insulin gene transfer. These tissues are selected because of their accessibility, regenerative capacity, and ability to produce therapeutic proteins. Using viral or non-viral gene delivery systems, the insulin gene is introduced into these cells, which are often further engineered with glucose-responsive regulatory elements to ensure that insulin secretion closely mimics the body's natural physiological response. This strategy has shown promising results in experimental studies by improving glycemic control, reducing hyperglycemia, and decreasing the need for repeated exogenous insulin injections. Although insulin gene therapy remains under clinical investigation, advances in gene delivery technologies and gene regulation systems continue to enhance its potential as a long-term treatment for both Type 1 and Type 2 diabetes mellitus (Goldman and Poss, 2020) [13].

2. β-Cell Regeneration

β-Cell regeneration is a promising gene therapy strategy aimed at restoring the body's natural ability to produce insulin by increasing the number of functional pancreatic β-cells. In both Type 1 and advanced Type 2 diabetes mellitus, the loss or dysfunction of β-cells leads to insufficient insulin secretion and poor glycemic control. Gene therapy seeks to overcome this problem by delivering genes that encode key pancreatic transcription factors, such as Pancreatic and Duodenal Homeobox-1 (PDX-1), Neurogenin-3 (NGN3), and MafA, which play essential roles in pancreatic development, β-cell differentiation, and insulin gene expression. The expression of these transcription factors can stimulate the differentiation of stem cells or pancreatic progenitor cells into mature, insulin-producing β-cells and may also promote the regeneration of existing pancreatic tissue. Experimental studies have demonstrated that this approach can enhance β-cell mass, improve endogenous insulin production, and restore glucose homeostasis in diabetic animal models. When combined with stem cell therapy and advanced gene delivery systems, β-cell regeneration has the potential to provide a long-lasting and

potentially curative treatment for diabetes mellitus by replacing the damaged or destroyed insulin-producing cells (Abdalla *et al*., 2024) [1].

3. Protection of β-Cells

Protection of pancreatic β-cells is an important gene therapy strategy aimed at preserving the function and survival of insulin-producing cells by reducing cellular damage caused by inflammation, oxidative stress, and apoptosis. In both Type 1 and Type 2 diabetes mellitus, β-cells are exposed to inflammatory cytokines, reactive oxygen species (ROS), and metabolic stress, leading to progressive cell dysfunction and death. Gene therapy can enhance β-cell survival by delivering genes that encode anti-apoptotic and antioxidant proteins. Examples include B-cell lymphoma 2 (Bcl-2), which inhibits programmed cell death (apoptosis); Heme Oxygenase-1 (HO-1), which provides anti-inflammatory, antioxidant, and cytoprotective effects; and Superoxide Dismutase (SOD), an antioxidant enzyme that neutralizes harmful free radicals and reduces oxidative stress. By increasing the expression of these protective proteins, gene therapy helps preserve β-cell integrity, maintain insulin secretion, and slow the progression of diabetes. This strategy may be particularly beneficial when combined with immune-modulating therapies or β-cell regeneration approaches, offering a comprehensive method for improving long-term pancreatic function and glycemic control (Dinić *et al*., 2022) [9].

4. Immune Modulation

Immune modulation is a key gene therapy strategy for the treatment of Type 1 diabetes mellitus (T1DM), an autoimmune disease in which the body's immune system mistakenly attacks and destroys insulin-producing pancreatic β-cells (Mittal *et al*., 2025) [26]. The primary goal of immune-modulating gene therapy is to suppress the harmful autoimmune response while preserving normal immune function, thereby preventing further β-cell destruction and maintaining endogenous insulin production. This approach involves delivering genes that encode immunoregulatory molecules such as Interleukin-10 (IL-10), an anti-inflammatory cytokine that suppresses immune activation; Transforming Growth Factor-β (TGF-β), which promotes immune tolerance and inhibits inflammatory responses; and CTLA4-Ig, a fusion protein that blocks T-cell activation by interfering with co-stimulatory signaling. Another promising strategy involves enhancing the number or function of regulatory T cells (Tregs), which play a critical role in maintaining immune tolerance and preventing autoimmune reactions against pancreatic β-cells. By reducing inflammation, inhibiting autoreactive immune cells, and promoting immune tolerance, these gene therapy approaches aim to preserve residual β-cell mass, delay disease progression, and reduce or eliminate the need for lifelong insulin therapy. Although immune modulation has shown encouraging results in experimental studies and early clinical trials, further research is needed to establish its long-term safety, efficacy, and clinical applicability (Li and He, 2004).

5. Improving Insulin Sensitivity

Improving insulin sensitivity is an important gene therapy strategy for the treatment of Type 2 diabetes mellitus (T2DM), where insulin resistance is the primary underlying defect. In T2DM, target tissues such as skeletal muscle, liver, and adipose tissue become less responsive to insulin, resulting in impaired glucose uptake and persistent hyperglycemia. Gene therapy aims to enhance insulin signaling pathways by delivering therapeutic genes that improve the cellular response to insulin and restore normal glucose metabolism. Key molecular targets include Glucose Transporter Type 4 (GLUT4), which facilitates insulin-dependent glucose uptake into muscle and adipose tissues; Peroxisome Proliferator-Activated Receptor Gamma (PPAR-γ), a nuclear receptor that regulates glucose and lipid metabolism while enhancing insulin sensitivity; Insulin Receptor Substrate-1 (IRS-1), an essential signaling protein that transmits signals from the insulin receptor to downstream pathways; and the Akt signaling pathway, which plays a central role in promoting glucose uptake, glycogen synthesis, and cell survival. Enhancing the expression or activity of these genes through gene therapy can improve insulin responsiveness, increase glucose utilization by peripheral tissues, reduce hepatic glucose production, and lower blood glucose levels. Consequently, this approach has the potential to improve glycemic control, reduce metabolic complications, and decrease the progression of Type 2 diabetes, although further clinical studies are needed to establish its long-term safety and therapeutic effectiveness (Khan *et al*., 2025) [17].

6. Gene Editing

Gene editing is an advanced and rapidly evolving gene therapy strategy that enables precise modification of DNA sequences to correct disease-causing genetic abnormalities (Li *et al*., 2020) [13]. The development of Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-Cas9 technology has revolutionized gene therapy by providing a highly accurate, efficient, and cost-effective method for editing specific genes within living cells. In diabetes mellitus, gene editing has several promising applications, including the correction of diabetes-associated genetic mutations, editing immune cells to prevent autoimmune destruction of pancreatic β-cells, enhancing β-cell survival and function, and engineering stem cells to differentiate into functional insulin-producing β-cells for transplantation. CRISPR-Cas9 can precisely target and modify specific DNA sequences by introducing, deleting, or replacing genetic material, thereby correcting defective genes or regulating gene expression. Experimental studies have demonstrated that CRISPR-based approaches can improve insulin secretion, preserve β-cell mass, and restore glucose homeostasis in animal models of diabetes. Despite these encouraging findings, challenges such as off-target effects, efficient delivery to target tissues, immune responses, and long-term safety remain to be addressed before gene editing can become a routine clinical treatment for diabetes. Nevertheless, continued advances in CRISPR technology and other genome-editing tools hold great promise for developing personalized, long-lasting, and potentially curative therapies for both Type 1 and Type 2 diabetes mellitus (Huang *et al*., 2022) [14].

7. Stem Cell-Based Gene Therapy

Stem cell-based gene therapy is an emerging regenerative approach that combines the self-renewal and differentiation capabilities of stem cells with the precision of gene therapy to restore pancreatic β-cell function in patients with diabetes mellitus (Ghassemifard *et al*., 2025) [12]. This strategy aims to generate healthy, functional insulin-producing β-cells by genetically modifying stem cells before or after

transplantation. Various stem cell sources have been investigated, including embryonic stem cells (ESCs), which possess unlimited differentiation potential; induced pluripotent stem cells (iPSCs), which are reprogrammed from adult somatic cells and offer the advantage of patient-specific therapy with reduced risk of immune rejection; mesenchymal stem cells (MSCs), known for their immunomodulatory, anti-inflammatory, and tissue repair properties; and adult pancreatic progenitor cells, which have the ability to differentiate into pancreatic cell lineages. Through gene transfer or genome-editing techniques, these stem cells can be engineered to express key transcription factors and regulatory genes that promote their differentiation into mature, insulin-producing β-cells while enhancing their survival, functionality, and resistance to immune-mediated destruction. Once transplanted into the patient, these gene-modified cells have the potential to restore endogenous insulin secretion, improve glucose homeostasis, and reduce or eliminate the need for lifelong insulin therapy. Although stem cell-based gene therapy has demonstrated promising results in preclinical studies and early clinical trials, challenges such as ensuring long-term cell survival, preventing immune rejection, minimizing the risk of tumor formation, and optimizing gene delivery methods must be overcome before this approach can be widely adopted in clinical practice. Nevertheless, continued advances in stem cell biology, gene editing, and regenerative medicine suggest that stem cell-based gene therapy may become a transformative and potentially curative treatment for both Type 1 and Type 2 diabetes mellitus (Sadhu *et al*., 2025) [26].

Future Perspectives

The future of gene therapy for diabetes mellitus is highly promising, driven by rapid advances in molecular biology, nanotechnology, artificial intelligence (AI), stem cell research, and genome-editing technologies. These innovations are facilitating the development of safer, moreefficient, and highly targeted therapeutic strategies that address the underlying causes of diabetes rather than merely controlling its symptoms. One of the most significant future directions is personalized gene therapy, in which treatment is tailored to an individual's genetic profile, disease characteristics, and therapeutic response, thereby maximizing efficacy while minimizing adverse effects. Advances in viral and non-viral gene delivery systems are expected to improve the precision, efficiency, and safety of therapeutic gene transfer to target tissues such as pancreatic β-cells, liver, skeletal muscle, and adipose tissue. Furthermore, combination therapies integrating gene therapy with stem cell transplantation and genome-editing technologies have the potential to regenerate functional insulin-producing β-cells and provide long-term restoration of endogenous insulin secretion. The development of *in vivo* β-cell regeneration strategies, which stimulate the body's own pancreatic cells to regenerate without the need for transplantation, represents another exciting area of research. Additionally, precision medicine approaches that integrate genomic, proteomic, and clinical data are expected to enable individualized treatment plans and improve therapeutic outcomes. Researchers are also developing glucose-responsive insulin gene systems, capable of sensing changes in blood glucose concentrations and automatically regulating insulin production, thereby closely mimicking normal physiological insulin secretion. At the same time, continuous improvements in CRISPR-based genome-editing technologies, including high-fidelity and next-generation gene editors, are expected to enhance editing accuracy, reduce off-target effects, and improve long-term safety. Although several scientific, technical, ethical, and regulatory challenges remain, ongoing research and clinical trials continue to expand the potential applications of gene therapy. As these technologies mature, gene therapy may transform diabetes management from lifelong symptomatic treatment to durable disease modification and, ultimately, provide a safe, effective, and potentially curative therapy for both Type 1 and Type 2 diabetes mellitus.

Table 1: Gene Therapy Strategies for Diabetes Mellitus: Summary of Previous Published Studies

Gene Therapy Strategy	Mechanism of Action	Target Diabetes Type	Key Findings from Previous Studies	Advantages	Limitations	References
Insulin Gene Therapy	Introduction of insulin gene into liver, skeletal muscle, or other non-β cells to produce insulin	T1DM, Advanced T2DM	Demonstrated sustained insulin production and improved glycemic control in preclinical models	Long-term insulin secretion; reduces dependence on insulin injections	Difficulty in physiological glucose-responsive insulin release	Wong *et al*. (2010); Xie *et al*. (2025); Khan *et al*. (2025) [33, 34]
β-Cell Regeneration Gene Therapy	Activation of genes regulating β-cell proliferation and regeneration (PDX1, NGN3, MAFA)	T1DM, T2DM	Promotes regeneration of pancreatic β-cells and restoration of insulin secretion	Restores endogenous insulin production	Limited regenerative capacity and immune-mediated destruction	Abdalla (2024); Goldman & Poss (2020); Addissouky (2025) [1, 2, 13]
CRISPR/Cas9 Gene Editing	Precise editing of disease-causing genes using CRISPR-Cas9 technology	Monogenic diabetes, T1DM, T2DM	High gene-editing efficiency with potential correction of genetic mutations	Permanent correction of pathogenic mutations	Off-target mutations, ethical concerns, delivery challenges	Huang *et al*. (2022); Li *et al*. (2020); Mulvihill *et al*. (2017) [14, 19, 23]
Immune-Modulating Gene Therapy	Delivery of immunoregulatory genes (IL-10, TGF-β, FOXP3) to suppress autoimmune destruction	T1DM	Delays autoimmune β-cell destruction and preserves residual β-cell function	Disease-modifying potential	Long-term immune safety remains uncertain	Mittal *et al*. (2025) [22]; Li & He (2004); Warshauer *et al*. (2020) [31]
Stem Cell–Gene Combination Therapy	Genetically modified stem cells differentiate into insulin-producing	T1DM, T2DM	Improved β-cell survival and insulin secretion in experimental studies	Regenerative and personalized treatment	High cost; risk of tumorigenesis and immune rejection	Sadhu *et al*. (2025); Ghassemifard *et al*.

	β-like cells					(2025); Addissouky (2025) [2, 12, 26]
RNA-Based Gene Therapy	siRNA, miRNA, and mRNA regulate genes involved in insulin secretion and insulin resistance	Mainly T2DM	Modulates glucose metabolism and improves insulin sensitivity	High specificity and reversible action	Short half-life and delivery instability	Khan *et al*. (2025); Ghassemifard *et al*. (2025) [12, 17]
Viral Vector Gene Delivery	Adeno-associated virus (AAV), lentivirus, and adenovirus deliver therapeutic genes	T1DM, T2DM	High transduction efficiency and prolonged gene expression	Efficient and stable gene transfer	Immunogenicity and insertional mutagenesis risks	Geng *et al*. (2025); Verma & Weitzman (2005) [11, 30]
Non-Viral Vector Gene Delivery	Lipid nanoparticles, polymers, plasmids, and nanoparticles transport genes	T1DM, T2DM	Improved safety profile compared with viral vectors but lower transfection efficiency	Reduced immune response and greater safety	Lower gene delivery efficiency	Geng *et al*. (2025); Budreviciute *et al*. (2020) [6, 11]
Gene Therapy for Diabetic Complications	Targeting oxidative stress, inflammation, endothelial dysfunction, and organ damage	T1DM, T2DM	Experimental therapies reduce diabetic nephropathy, hepatic injury, and vascular complications	May prevent long-term diabetic complications	Mostly preclinical evidence	Yan *et al*. (2024); Dinić *et al*. (2022); Lodi *et al*. (2026) [9, 21, 36]
Precision Medicine and Personalized Gene Therapy	Patient-specific genetic profiling guides individualized therapy	Monogenic diabetes (MODY), T1DM, T2DM	Enables tailored treatment based on genetic background	Improved efficacy and fewer adverse effects	High cost and need for advanced genomic testing	Khan *et al*. (2026); Zagaroli *et al*. (2026); Davies *et al*. (2026) [7, 35, 37]

Conclusion

Gene therapy represents one of the most promising emerging strategies for the treatment of diabetes mellitus. By targeting the molecular and genetic mechanisms underlying the disease, it has the potential to restore insulin production, regenerate pancreatic β-cells, enhance insulin sensitivity, and modulate autoimmune responses. Although significant scientific, technical, ethical, and regulatory challenges remain, advances in viral vectors, genome editing, and stem cell technologies continue to move the field forward. Continued basic research, carefully designed clinical trials, and long-term safety evaluations will determine the ultimate role of gene therapy in diabetes management. With ongoing innovation, gene therapy may eventually provide durable, personalized, and potentially curative treatments for both Type 1 and Type 2 diabetes.

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