www.ijarp.com ISSN 2456-9992 Page: 01-07

International Journal Advanced Research Publications

Review Article

Volume: 02
Issue: 03

NEW TREATMENT APPROACHES FOR DIABETES MELLITUS

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Article Received: 27 January 2026, Article Revised: 15 February 2026, Published on: 07 March 2026

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DOI: https://doi-doi.org/101555/ijarp.7570

ABSTRACT

Diabetes mellitus (DM) is a complex metabolic disorder characterized by chronic hyperglycemia due to defects in insulin secretion, action, or both. The global prevalence of DM is increasing rapidly, with Type 2 diabetes accounting for the majority of cases worldwide. Conventional therapies such as insulin and oral hypoglycemic agents have improved glycemic control but are limited by side effects, patient compliance issues, and inability to fully prevent long-term complications. Recently, novel treatment approaches — including incretin-based therapies, sodium-glucose co-transporter 2 (SGLT2) inhibitors, dual/triple agonists, β-cell regeneration strategies, immunotherapy for Type 1 diabetes, stem cell–based islet replacement, closed-loop insulin delivery systems, and microbiome modulation — have emerged. This review discusses these evolving therapies, their mechanisms, clinical efficacy, limitations, and future prospects in the management of diabetes mellitus.

KEYWORDS: Diabetes mellitus, incretin therapy, SGLT2 inhibitors, β-cell regeneration, immunotherapy, artificial pancreas, stem cell therapy.

1. INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder with progressive hyperglycemia resulting from impaired insulin secretion, insulin action, or both. It is classified mainly into:

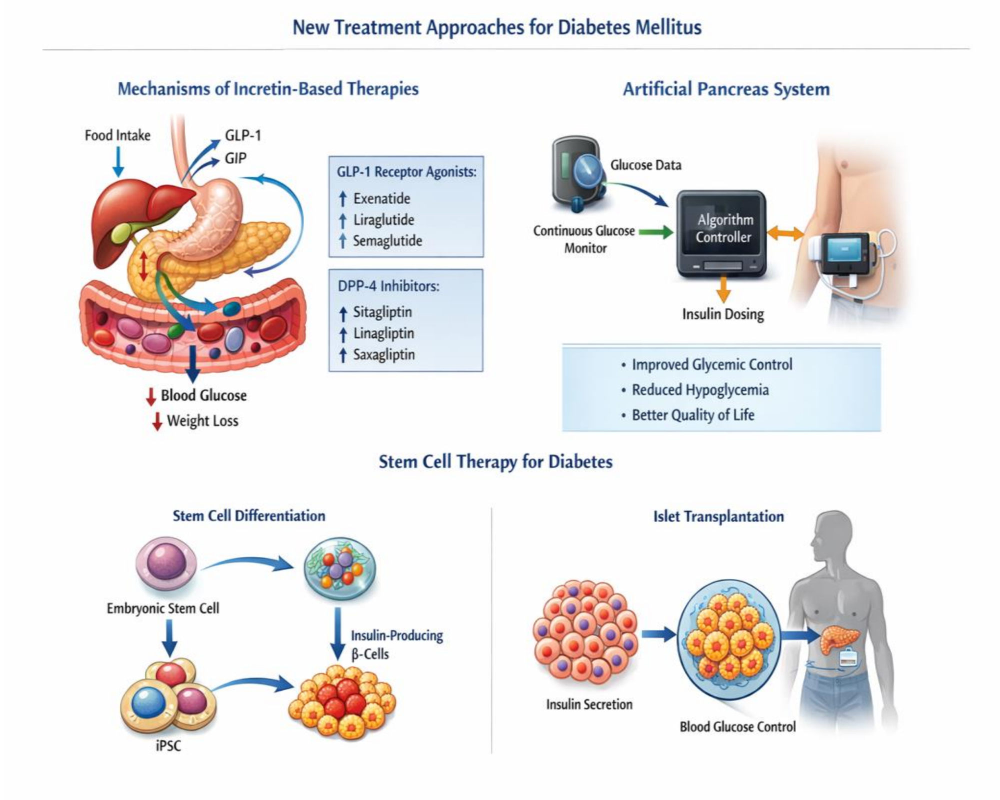
Type 1 Diabetes Mellitus (T1DM): Autoimmune β-cell destruction leading to absolute insulin deficiency.

Type 2 Diabetes Mellitus (T2DM): Insulin resistance with relative insulin deficiency.

Gestational Diabetes Mellitus (GDM): Hyperglycemia first recognized during pregnancy.

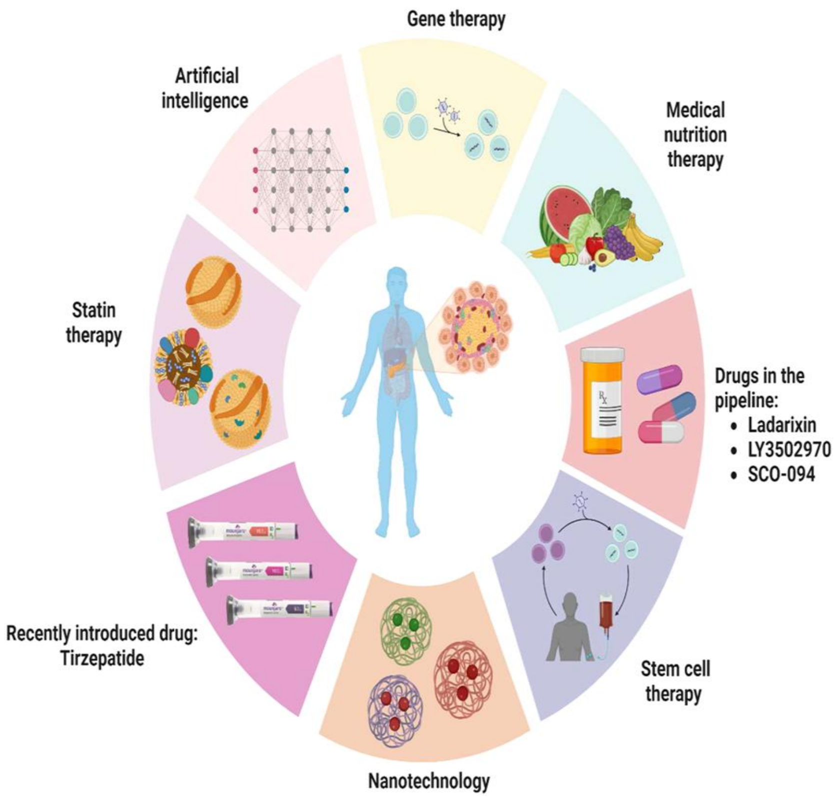
According to the International Diabetes Federation, the number of adults with diabetes was estimated to be over 537 million in 2021, with projections exceeding 780 million by 2045, highlighting the urgent need for improved therapeutic strategies.^1

Conventional therapies for diabetes include lifestyle modification, insulin, and oral antidiabetic drugs (metformin, sulfonylureas, thiazolidinediones). Although effective in lowering blood glucose, these treatments often fail to prevent microvascular and macrovascular complications and may cause side effects such as hypoglycemia and weight gain.^2 Therefore, research has shifted toward interventions that provide glycemic control and target underlying pathophysiological mechanisms, preserve β-cell function, improve metabolic outcomes, and reduce long-term complications.



2. PATHOPHYSIOLOGICAL BASIS FOR NOVEL THERAPIES

The pathogenesis of T2DM involves multiple defects: Insulin resistance in muscle, liver, and adipose tissue Progressive β-cell dysfunction and apoptosis Abnormal glucagon secretion by α-cells Increased renal glucose reabsorption Chronic low-grade inflammation Understanding these mechanisms has led to the development of targeted therapies beyond traditional glucose lowering.^3



3. INCRETIN-BASED THERAPIES

3.1 GLP-1 Receptor Agonists

Glucagon-like peptide-1 (GLP-1) is an incretin hormone released from intestinal L-cells after meals that enhances glucose-dependent insulin secretion, suppresses glucagon release, delays gastric emptying, and promotes satiety. GLP-1 receptor agonists (e.g., exenatide, liraglutide, dulaglutide, semaglutide) mimic endogenous GLP-1 but have longer half-lives.^4

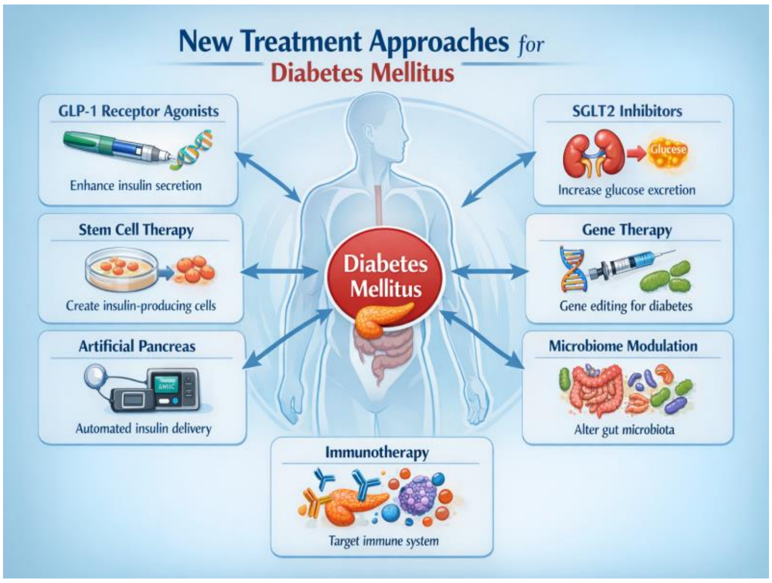
Clinical trials have shown GLP-1 receptor agonists significantly reduce HbA1c and body weight, with additional cardiovascular benefits in high-risk patients. They also have a low risk of hypoglycemia due to glucose-dependent action.^5

3.2 Dual Incretin Agonists

Tirzepatide, a glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor co-agonist, has demonstrated superior glycemic control and weight reduction compared to traditional GLP-1 agonists in head-to-head trials.^6 This dual mechanism enhances insulin secretion, suppresses glucagon, and improves insulin sensitivity.

3.3 Triple Agonists

Emerging research focuses on triple agonists targeting GLP-1, GIP, and glucagon receptors. Preclinical studies suggest potential for greater metabolic improvements, weight reduction, and β-cell preservation than dual agonists.^7 However, human data remain limited.



4. SODIUM-GLUCOSE CO-TRANSPORTER INHIBITORS

4.1 SGLT2 Inhibitors

SGLT2 inhibitors (e.g., empagliflozin, canagliflozin, dapagliflozin) reduce renal glucose reabsorption, leading to increased glucosuria and lower plasma glucose levels independent of insulin action. They also produce modest weight loss and lower blood pressure.^8

Large cardiovascular outcome trials (e.g., EMPA-REG, CANVAS, DECLARE-TIMI 58) have shown these agents significantly reduce major adverse cardiovascular events (MACE), heart failure hospitalizations, and progression of diabetic kidney disease, establishing them as cardio-renal protective therapies.^9

4.2 Dual SGLT1/SGLT2 Inhibition

Dual inhibition of SGLT1 (intestinal) and SGLT2 (renal) receptors can reduce both renal glucose reabsorption and intestinal glucose absorption, potentially enhancing glycemic control and incretin secretion. Sotagliflozin is one such dual inhibitor studied in clinical trials, exhibiting benefits in glycemic control and heart failure outcomes.^10

5. BETA-CELL PRESERVATION AND REGENERATION STRATEGIES

Progressive β-cell loss is central to T2DM pathogenesis. New therapeutic strategies aim to preserve or regenerate β-cell mass:

5.1 Beta-Cell Regenerative Agents

Research is exploring small molecules and peptides that stimulate β-cell proliferation and differentiation from progenitor cells. Agents like harmine derivatives have shown potential in preclinical models by activating the DYRK1A pathway, increasing human β-cell replication.^11

5.2 Gene Therapy

Gene therapy targeting key transcription factors and signaling pathways involved in β-cell survival and function represents a promising area. Experimental approaches include delivery of genes that enhance insulin production or protect β-cells from apoptosis.^12

6. IMMUNOTHERAPY FOR TYPE 1 DIABETES

T1DM results from autoimmune destruction of pancreatic β-cells. Traditional management relies on lifelong insulin therapy, but immunotherapeutic approaches aim to modify disease progression:

6.1 Anti-CD3 Monoclonal Antibodies

Teplizumab, a humanized anti-CD3 monoclonal antibody, has been shown to delay the onset of clinical diabetes in high-risk individuals by modulating autoreactive T-cells and preserving residual β-cell function.^13

6.2 Antigen-Specific Immunotherapy

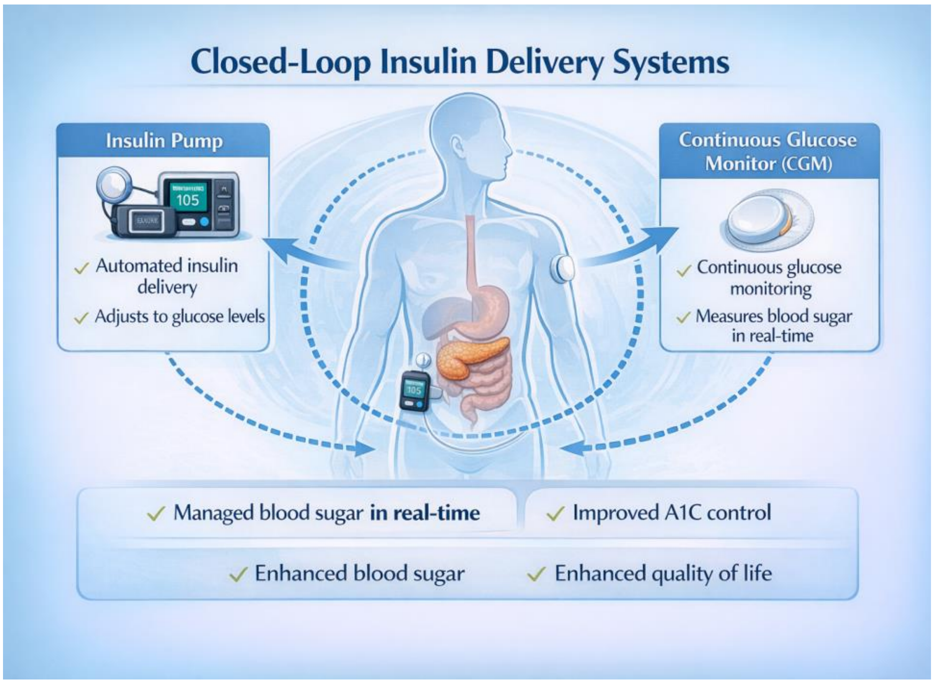
Vaccines targeting specific β-cell antigens (e.g., GAD65) are under investigation to induce immune tolerance and prevent autoimmune attack. Early trials have shown promise but require further validation.^14

7. STEM CELL-BASED ISLET REPLACEMENT THERAPY

Replacement of destroyed β-cells using stem cell–derived islets offers potential for durable insulin independence. Pluripotent stem cells can be differentiated into insulin-producing cells and encapsulated to prevent immune rejection. Early clinical studies demonstrate safety and some efficacy, though challenges remain in immunoprotection and long-term viability.^15

8. CLOSED-LOOP INSULIN DELIVERY SYSTEMS

Advances in diabetes technology have led to closed-loop “artificial pancreas” systems that integrate continuous glucose monitoring (CGM) with automated insulin delivery via algorithms. These systems adjust insulin dosing in real time, improving time-in-range and reducing hypoglycemia in T1DM patients.^16



9. GUT MICROBIOME MODULATION

Emerging evidence links gut microbiota composition with insulin sensitivity and metabolic regulation. Research suggests that modulation of gut flora through prebiotics, probiotics, or microbiota transplantation may influence glucose metabolism, though more robust clinical evidence is needed.^17

10. DISCUSSION

Recent advancements in diabetes treatment reflect a shift from simplistic glucose lowering toward comprehensive metabolic modulation and disease modification. Incretin-based therapies and SGLT2 inhibitors have reshaped clinical practice by offering cardiovascular and renal benefits beyond glycemic control. Regenerative and immunomodulatory therapies present prospects for altering disease progression, particularly in early T1DM and β-cell failure. Technological tools such as artificial pancreas systems enhance quality of life and glycemic stability. However, access, cost, long-term safety, and patient adherence remain challenges. Continued translational and clinical research is essential for integrating these innovations into routine care.

11. CONCLUSION

Diabetes mellitus management has evolved significantly with the development of novel therapies targeting multiple pathophysiological facets of the disease. These advances hold promise for more effective glycemic control, complication reduction, and potential disease modification. A comprehensive understanding of these approaches is crucial for pharmacy professionals involved in therapy optimization and patient education.

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