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NEXT GENERATION ANTIDIABETIC THERAPIES: RECENTLY APPROVED DRUGS AND PIPELINE INNOVATIONS

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ABSTRACT

Diabetic Mellitus, a chronic metabolic disorder, continuous to pose significant Health challenges globally. The management of diabetes mellitus has entered a transformative era with the advent of novel pharmacological agents and advanced drug delivery systems that aim to optimize glycemic control, reduce complications, and improve patient adherence. This article aims to provide a comprehensive review of the latest clinical trials, FDA approvals and ongoing research drugs on diabetes management and novel approaches like Artificial Pancreas System. The potential impact of immunomodulatory therapies and Beta cell regeneration strategies, including the management of Diabetes in pediatrics with recent technologies are also explored. Among the most promising therapies is tirzepatide, a dual GIP/GLP-1 receptor agonist that demonstrates superior efficacy in reducing HbA1c and body weight compared to conventional agents. The advent of once-weekly basal insulins such as insulin icodec and efsitora alfa signifies a paradigm shift in insulin therapy, reducing injection burden while maintaining stable glycemic profiles. Additionally, Lantidra, the first FDA-approved allogeneic pancreatic islet cell therapy, offers a functional cure for select patients with type 1 diabetes, eliminating the need for exogenous insulin. The investigational compound harmine, known for its DYRK1A inhibitory properties, shows promise in stimulating human β-cell proliferation, potentially enabling endogenous insulin regeneration. Emerging therapies like Merilog and TIX-100, though in earlier stages, represent next-generation molecules targeting unique pathways for improved glycemic and metabolic outcomes. Together, these advances underscore a shift towards personalized, patient-centric diabetes management, with a focus on long-term efficacy, safety, and quality of life improvements.

INTRODUCTION

Diabetes mellitus is a prevalent comorbidity associated with increased healthcare burden, reduced patient well-being, and elevated mortality rates [1]. Diabetes affected 10.5% of adults (536.6M) in 2021 and is projected to reach 12.2% (783.2M) by 2045, with higher rates in older adults, urban areas, and wealthier countries[2]. Diabetes persists as a significant concern in healthcare systems globally. Type 2 diabetes, the most common and often preventable form, is increasing globally due to rising obesity or driven by various factors. Early detection can reverse it in some cases, but prevention remains challenging. Understanding population-specific risk and burden is vital for effective control strategies[3]. Type 1 and type 2 diabetes significantly impact both public health and economic stability in communities [4,5]. According to Ho Municipality, Ghana a hospital-based cross-sectional study was carried and reported that Engaging in moderate physical activity may improve both glycaemic control and blood pressure management [5]. While physical activity provides significant health benefits for people with diabetes, high rates of inactivity remain common in this population[6]. Countries with large adult populations also have the highest diabetes numbers, with China (98.4M) and India (65.1M) leading. Eight of the ten most populous nations are also among the top ten for adult diabetes cases. Diabetes prevalence rises with age in all regions and income groups, peaking at 18.6% in those aged 60–79. However, most cases (184 million) are in the 40–59 age group, a trend expected to continue over the next 20 years[7].Rising diabetes rates globally are linked to modern lifestyles, sedentary habits, hereditary , dietary shifts, increasing Urbanisation , obesity, Socioeconomic Disparities and other various conditions [8-10]. Diabetes can lead to or enhance the risk of several other serious health conditions due to prolonged high blood sugar levels and metabolic imbalances which include Cardiovascular diseases'(like myocardial infarction, stroke and heart failure)[11],Kidney Disease (Diabetic Nephropathy is a leading cause of end-stage renal disease (ESRD) [12], Eye Disorders (Diabetic Retinopathy) [13],Nerve Damage (Diabetic Neuropathy) [14],Diabetic foot ulcers [15], Skin infections [16], Alzheimer's Disease and Cognitive Decline [17],dental problems (Periodontitis) [18], Depression and Mental Health Issues[19]. Type 2 diabetes accounts for over 95% of all diabetes cases globally. In 2017, it affected around 462 million people, representing 6.28% of the world's population. While less common, type 1 diabetes is increasing, particularly among children and adolescents. The number of individuals under 20 years living with type 1 diabetes is estimated to be over 1.5 million globally. Projections indicate that the number of adults with diabetes will increase from 537 million in 2021 to 783 million by 2045[20,21]. In recent years, advancements in diabetes management and treatment have ushered in a new era of therapeutic options, ranging from cutting-edge medications to innovative technologies. Among the most promising treatments,Tirzepatide[22],Merilog[30],Orforg lipron[32], Lantidra[34], Ozempic[36], and TIX100[44] stand out as potent contenders in the fight against type 2 diabetes and weightloss. These therapies represent significant strides in the development of medications that target the underlying mechanisms of the disease. Meanwhile, long-acting insulin formulations such as Insulin Icodec and Insulin Efsitora are redefining how insulin therapy can be delivered to enhance patient outcomes with less frequent dosing[49,55]. In addition to pharmaceutical advancements, the artificial pancreas system has emerged as a breakthrough in personalized diabetes care, offering automated glucose control for those with type 1 diabetes [96].On the horizon, natural and cell-based therapies, including the use of Harmine, are being explored for their potential to regenerate pancreatic cells and restore insulin production[86]. These novel approaches, combined with sophisticated technologies, are setting the stage for a future where diabetes management may become more effective, personalized, and less invasive. This article delves into the most recent innovations in diabetes therapy, providing an overview of their mechanisms, benefits, and future potential[97].

NOVEL THERAPIES FOR DIABETES MELLITUS:

1. **TIRZEPATIDE:** Tirzepatide (Mounjaro), developed by Eli Lilly and approved by the FDA in May 2022, is the first dual GLP-1 and GIP receptor agonist ("twincretin") that significantly lowers blood glucose, improves insulin sensitivity and lipid metabolism, and reduces body weight by over 20%. As a synthetic GIP analog with acylation for albumin binding, it enables once-weekly subcutaneous dosing, ushering in a new era of dual therapies for diabetes, obesity, and cardiometabolic diseases[22]. Tirzepatide demonstrated safety and efficacy for weight management in adults with T1D, leading to significant weight loss, reduced insulin doses, and improved glycemic control over 8 months. Additionally, three years of tirzepatide treatment in individuals with obesity and prediabetes sustained substantial weight

loss and significantly reduced progression to type 2 diabetes compared to placebo [23,24]. Further research is warranted to understand subgroup differences in glycemic responses and outcomes in older, frail populations. In the SURMOUNT-2 trial, tirzepatide significantly improved physical and psychosocial HRQoL in participants with obesity and T2D, with greater benefits seen in those achieving more weight loss and those with baseline physical limitations [25,26]. Additional advantages: Tirzepatide improves hemodynamics, reduces blood pressure, circulatory volume expansion, systemic inflammation, myocardial injury and enhances renal and functional outcomes in obesity-related HFpEF, offering sustained and multifaceted clinical benefits [27-29].

2. **MERILOG:**The FDA approved Merilog (insulin-aspart-szjj) as the first rapid-acting insulin recently in february 2025 which is biosimilar to Novolog for improving glycemic control in adults and children with diabetes[30]. Available in prefilled pens and vials, Merilog is administered subcutaneously within 5–10 minutes before meals, with individualized dosing based on patient needs. It is designed to manage mealtime blood sugar that enhances glycemic control and is offered in both a 3 mL single-patient-use pen and a 10 mL vial for multiple doses.[30]
3. **Orforglipron:** Orforglipron, a non-peptide oral GLP-1 receptor agonist, shows promising efficacy in the treatment of type 2 diabetes mellitus (T2DM). Meta-analysis results indicate that Orforglipron significantly reduces HbA1c and fasting plasma glucose (FPG) levels compared to placebo, although weight loss benefits are less consistent. Gastrointestinal side effects (nausea, vomiting, diarrhea) were common, particularly during dose escalation, though no clear dose-dependent pattern was observed in early-phase trials, likely due to small sample sizes. Unlike injectable or peptide-based therapies, Orforglipron offers improved bioavailability without fasting requirements, enhancing its clinical convenience. These findings suggest Orforglipron has strong potential as a future oral therapy for T2DM, though larger and longer studies are needed to confirm its long-term efficacy and safety[32].After 12 weeks, Orforglipron significantly reduced HbA1c, fasting glucose, and body weight, with a safety profile similar to other GLP-1RAs and convenient once-daily oral dosing without food or water restrictions, offering a promising treatment for T2D and other conditions [31].Orforglipron demonstrated a favorable safety profile across clinical trials, with mild to moderate gastrointestinal events as the most common adverse reactions. Pharmacokinetic studies reported a half-life between 29–67.5 hours, supporting once-daily dosing without food restrictions. In Phase Ia and Ib trials, Orforglipron led to significant weight loss (up to 5.8 kg) and HbA1c reductions (1.5–1.8%) over 12 weeks in T2DM patients. Phase II trials showed even greater benefits, with HbA1c reductions of up to 2.10% and weight losses of 9.4% to 14.7% in both diabetic and non-diabetic obese patients, positioning Orforglipron as a promising oral therapy for T2DM and obesity[33].
4. **LANTIDRA**: The FDA approved **Lantidra**, the first cellular therapy made from deceased donor pancreatic cells, for adults with type 1 diabetes who struggle to control HbA1c due to recurrent severe hypoglycemia. Administered via a single infusion into the hepatic portal vein, Lantidra enables donor beta cells to produce insulin, potentially eliminating the need for injections. In two nonrandomized studies of 30 patients, 21 stopped insulin use for at least one year, with 10 remaining insulin-free for over five years[34]. The future of islet transplantation, including Lantidra, holds both challenges and opportunities. While Lantidra is now covered by many U.S. private insurers and benefits from updated shipping protocols extending its shelf life to 48 hours, widespread adoption remains complex. In 2024, the University of Illinois Health began offering Lantidra therapy, with plans for multicenter expansion by 2025[35]. Although the FDA recently approved **Lantidra**, major barriers still prevent islet transplantation from becoming standard care for all type 1 diabetes patients [36].

Key challenges include donor islet scarcity, the need for systemic immunosuppression, high costs, and restrictive U.S. regulations that classify allogeneic islets as biologic drugs requiring costly BLA approval [37]. These regulatory constraints have led to a steep decline in islet transplantation procedures, 179 (1999–2005) to only 11 (2016–2019), in contrast to other countries that treat islets as minimally manipulated tissue and offer them as standard clinical care [38,39]. Experts propose regulatory updates to improve access, affordability, and outcomes for patients with severe hypoglycemia [40].

5. **OZEMPIC:** A GLP-1 receptor agonist, semaglutide has demonstrated meaningful weight loss in patients with type 2 diabetes [41]. Among high-risk patients, semaglutide significantly reduced rates of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke relative to placebo, confirming its cardiovascular noninferiority[42]. Furthermore, in patients with chronic kidney disease, semaglutide lowered the risk of critical kidney outcomes and cardiovascular death[43].
6. **TIX 100:** TIX100, a novel oral TXNIP inhibitor, protects against high-fat diet–induced glucose intolerance, hyperinsulinemia, hyperglucagonemia, and adiposity while preserving lean mass, without the liver and lipid abnormalities seen with some other agents**.** The observed enhancements in glucose homeostasis and reduction in glucagon levels mirrors the protective effects seen with genetic TXNIP deficiency and beta cell-specific TXNIP deletion in various diabetes models,[44] as well as decreased glucagon secretion following alpha cell TXNIP deletion,[45]and, unlike some glucagon receptor antagonists, enhances plasma cholesterol, triglycerides, and ALT levels without adverse liver effects[46]. TIX100, in high-fat diet (HFD) models, reduced weight gain and improved glucose metabolism (blood glucose, HbA1c, insulin, glucagon) without major weight loss. It enhanced leptin sensitivity, reduced food intake, and improved islet function while avoiding gastrointestinal side effects seen with GLP-1 agonists. Its metabolic effects were dependent on TXNIP, as they were lost in TXNIP-deficient mice. Unlike verapamil, TIX100 is safer, as it doesn’t affect calcium channels. TIX100 has the potential to serve as a novel oral therapy for managing both T1D and T2D**.** Preclinical studies show TIX100 is more potent than verapamil, metformin, and empagliflozin. Recently FDA-approved for clinical trials in T1D, TIX100 shows promise for diabetes treatment, focusing on islet preservation and glucose regulation[47].
7. **ONCE WEEKLY INSULIN (Insulin icodec, insulin efsitora alfa):** Insulin therapy has advanced over the past century, with once-weekly insulins like icodec and efsitora offering a significant breakthrough in basal insulin treatment [49]. Both create a circulating reservoir of insulin for sustained release, with icodec conjugated to HSA and efsitora using a novel insulin-IgG2 Fc fusion. These modifications reduce insulin's affinity for the insulin receptor (IR), slowing clearance and extending activity for weekly dosing [50].Icodec, with a half-life of 8 days, and efsitora, with a half-life of 17 days, provide similar efficacy to daily insulins with low hypoglycemia rates in T2D patients [51]. However, caution is needed for T1D patients until more data is available. Ongoing research, including CGM data, will provide more insights into their safety and effectiveness [52]. These insulins reduce injection burden, improve adherence, and may offer benefits such as fewer healthcare visits and more stable glucose control [53]. Additionally, the stable glucose profiles of weekly insulins could improve self-sufficiency in these patients, limit insulin titrations, and potentially reduce diabetic ketoacidosis (DKA) in non-compliant T1D patients, especially teenagers [54].

INSULIN ICODEC: Among 50 participants with T2D in a Phase 1 trial, icodec exhibited a median tmax of 16 hours and maintained a mean half-life of 8 days [55]. Participants received once-weekly icodec or daily IDeg, with glucose-lowering effects measured over 7 days. The response pattern remained consistent, with a modest rise observed on day 3 followed by a subtle decline on day 7 [56]. No serious adverse events or severe hypoglycemia were reported. A second study showed that icodec's exposure and glucose-lowering effects were consistent across different injection sites (thigh, abdomen, or upper arm)[57]. In Phase 2 studies on icodec in T2D patients explored dosing and titration strategies to inform phase 3 trials. In a 26-week trial of insulin-naive patients, icodec showed similar HbA1c reductions to daily IGlar U100, but with higher rates of level 1 hypoglycemia [58]. Another 16-week trial tested different titration approaches, finding the best balance of glycemic control and low hypoglycemia with a target glucose of 80-130 mg/dL and a weekly dose change of ±21 units [59]. A study on switching from daily basal insulins to weekly icodec showed that a loading dose improved time in range (TIR) and minimized transient hyperglycemia [60]. Overall, icodec demonstrated comparable efficacy to IGlar U100, with low hypoglycemia rates [61]. The use of a loading dose was particularly effective for patients transitioning to icodec[62]. The ONWARDS phase 3 program for icodec consisted of six clinical trials, focusing on T2D and T1D patients [63]. ONWARDS 1 to 5 were treat-to-target studies comparing icodec to once-daily insulins (IGlar U100, IDeg) and/or placebo, with ONWARDS 6 testing icodec in T1D patients [64]. Insulin doses were titrated to a prebreakfast glucose target of 80-130 mg/dL with specific adjustments for icodec and daily comparators [65]. The studies included insulin-naive (ONWARDS 1, 3, 5) and insulin-treated (ONWARDS 2, 4) populations. Starting doses for icodec were based on weekly totals, with some studies using a loading dose [66]. All studies met their primary endpoints of noninferiority to comparators for HbA1c reduction, with ONWARDS 1, 2, 3, and 5 showing statistically significant superiority in HbA1c reduction[67,68]. The ONWARDS 2 and 4 studies assessed the efficacy and safety of icodec compared to once-daily basal insulins (IDeg and IGlar U100) in patients with T2D[63,64].

ONWARDS 2 (26 weeks) showed that icodec reduced HbA1c from 8.2% to 7.2%, compared to 7.4% with IDeg, confirming noninferiority and superiority of icodec. An increase in hypoglycemia was evident with icodec, yet TBR measurements showed no meaningful variation. A modest increase in body weight (+1.4 kg with icodec vs −0.3 kg with IDeg) was noted, and patients preferred icodec based on treatment satisfaction scores[64,66].

ONWARDS 4 (26 weeks) showed similar HbA1c reductions (8.3% to 7.1% for both icodec and IGlar U100). Both groups maintained equivalent TIR and TAR values, yet level 1 hypoglycemia rates were elevated in the icodec group (31.5 vs 24.9 events per patient-year) [65,67]. The total insulin dose was lower for icodec, especially in the basal component, though body weight increases were similar between groups [69]. Post-hoc analyses revealed no significant differences in TIR or hypoglycemia duration at steady state[72,73].

ONWARDS 6 was a 52-week study comparing icodec and IDeg in type 1 diabetes patients. Icodec showed noninferiority to IDeg in HbA1c reduction (−0.37% vs −0.54%) at 52 weeks, but had significantly higher rates of combined level 2 or 3 hypoglycemia (19.93 vs 10.37 events per PYE) and nocturnal hypoglycemia. TIR and TAR were similar between the groups, with neither meeting guideline targets [55,68]. Icodec required higher basal insulin doses but lower bolus doses, with similar total weekly insulin doses between treatments. Body weight changes and overall treatment satisfaction favoured IDeg. The study suggests more research is needed, particularly using CGM-guided titration, to optimize icodec use in T1D and reduce hypoglycemia risk[70,71].

Clinical pharmacological studies: A study by Pieber et al. investigated hypoglycemia risk with icodec compared to IGlar U100 in patients with T2D, focusing on clinical, physiological, and counter regulatory responses to double and triple doses [74,75]. Both insulins caused similar rates of clinically significant hypoglycemia, but icodec showed faster recovery times, though the risk of recurrence remained due to its longer duration of action[76,77]. CGM data indicated low time spent in hypoglycemia after doses, even for those with significant hypoglycemia [78, 79]. Additional studies on renal and hepatic impairment indicated no major differences in icodec exposure, suggesting no dose adjustments are necessary for these populations [80,81]. Overall, practices for managing hypoglycemia with icodec are comparable to daily insulins [82], though further research in high-risk groups is recommended[83,84].

INSULIN EFSITORA: In Phase 1 studies, efsitora demonstrated glucose-lowering effects within 3 days of administration, with sustained fasting plasma glucose (FPG) reduction for at least 5 days. The pharmacokinetic (PK) profile showed peak concentration (tmax) at 4 days post-dose and a half-life of approximately 17 days[77].Hypoglycemic events with efsitora were similar to those seen with IGlar U100. In the multiple ascending dose (MAD) study, a loading dose strategy (3x weekly dose) accelerated time to steady-state concentration, and efsitora concentrations remained flat across all doses, showing a 14% increase in PK levels over a week[55].

In Phase 2 studies, efsitora was compared to insulin degludec (IDeg) and showed noninferiority in HbA1c reduction [78]. In T2D patients on basal insulin, efsitora had fewer hypoglycemic events and a lower weight gain (1.0 kg vs. 2.0 kg with IDeg) [79]. In insulin-naive T2D patients, efsitora also showed noninferiority in HbA1c reduction and had similar hypoglycemia rates compared to IDeg, with better time-in-range (TIR) and lower time-below-range (TBR) [80]. In T1D patients, efsitora was noninferior to IDeg in HbA1c reduction, with similar TIR and hypoglycemia rates. However, efsitora patients showed smaller weight gain (0.1 kg vs. 0.6 kg with IDeg) [81]. An initial period of hyperglycemia was observed in T1D patients due to potential underdosing, indicating the need for better dosing adjustments [82]. The ongoing Phase 3 QWINT trials are further investigating efsitora's efficacy, safety, and tolerability in T2D and T1D patients, comparing it with standard daily insulin regimens[85].

NATURAL AND CELL THERAPIES:

HARMINE: Harmine, a tricyclic β-carboline alkaloid from *Peganum harmala L.*, has attracted attention for its broad biological activities. Recent research (2019–2024) highlights the enhanced therapeutic potential of harmine derivatives. A comprehensive review of studies from major scientific databases explored their biological effects, structure–activity relationships, and emerging applications, including those involving nanotechnology. Notably, the biological activities of harmine contained antidiabetic properties [86]. *Peganum harmala*, through its key alkaloids harmine and harmaline, shows strong potential in regulating glucose homeostasis and enhancing insulin sensitivity [87]. Unlike synthetic GLP-1 receptor agonists like semaglutide, P. harmala stimulates the **endogenous secretion of GLP-1** by activating glucose-sensing pathways in enteroendocrine L-cells, primarily through **Akt/GLUT4 signaling**. This leads to increased GLUT4 translocation, glucose uptake, and GLP-1 exocytosis [88, 89]. Additionally, P. harmala activates the **Nrf2 antioxidant pathway**, reducing oxidative stress in L-cells and sustaining GLP-1 production. It also improves insulin sensitivity by enhancing **PI3K/Akt signaling** and reducing insulin resistance markers like pS307-IRS-1. Furthermore, inhibition of **GSK-3β** by harmine and harmaline enhances Nrf2 activity, reinforcing antioxidant defenses[90,91]. Thus, P. harmala acts as a dual therapeutic agent, improving insulin action and combating oxidative stress — both critical in diabetes and related neurodegenerative conditions [92]. Furthermore, structural modifications and the application of nanocarriers make harmine and its derivatives more druggable [86]. However, **low bioavailability** of harmine and harmaline remains a challenge to its clinical application [93,94].

BETA CELL REGENERATION VIA HARMINE: Harmine promotes β-cell proliferation via the DYRK1A-NFAT pathway but lacks selectivity. To improve this, 29 harmine analogs were synthesized, leading to the identification of **2-2c**, a novel DYRK1A inhibitor with enhanced selectivity, reduced CNS off-target effects, and superior β-cell regeneration efficacy at lower doses, making it a promising candidate for diabetes treatment[95].

ARTIFICIAL PANCREAS SYSTEM: Insulin therapy, essential for diabetes care, is evolving with wearable technologies like continuous glucose monitors (CGMs) and closed-loop insulin delivery systems [96]. Recent advances integrate artificial intelligence to enhance glucose control, aiming to create artificial pancreas systems [97]. While promising, challenges remain regarding device accuracy, algorithm safety, and data privacy [98]. Wearable devices and AI-driven systems are paving the way for more natural and responsive diabetes management, potentially transforming the treatment landscape for type 1 diabetes [99,100].

Wearable devices are transforming type 1 diabetes (T1D) management by enabling precise, real-time monitoring and insulin delivery without disrupting daily life [101]. Continuous glucose monitors (CGMs) track glucose levels dynamically, improving lifestyle management and reducing the need for frequent blood tests [102]. Advances include both electrochemical sensors and new noninvasive technologies like optical and electromagnetic methods [103,104]. In parallel, continuous subcutaneous insulin infusion (CSII) systems, such as smart insulin pens and pumps, offer more accurate and user-friendly insulin delivery, improving glycemic control, reducing hypoglycemia, and enhancing patient quality of life[105,106]. Wearable technologies have advanced CGM systems and insulin delivery, enabling the creation of closed-loop artificial pancreas (AP) systems that automate insulin dosing based on real-time glucose data[107]. These systems improve diabetes management and quality of life but still face risks like hypoglycemia and hyperglycemia. Accurate and adaptable prediction models are vital to address individual glucose variability [108]. Glucose prediction models use CGM data to forecast blood sugar trends and serve as early warning systems, but they must account for lifestyle and environmental factors[109,110]. Tools like Clarke Error Grid Analysis help evaluate prediction accuracy, though each method has specific strengths and limitations depending on the clinical goals [111]. Advances in glucose prediction have evolved from traditional mathematical models to data-driven machine learning (ML) and deep learning approaches [112]. Early models like AR, ARX, and ARMAX improved short-term forecasting accuracy but struggled with complex, nonlinear glucose dynamics [113]. Machine learning methods, including support vector regression (SVR) and random forests (RF), enhanced predictions by analyzing factors such as meals, insulin, and physical activity, achieving high accuracy (up to 94% for nocturnal hypoglycemia) [114,115]. Deep neural networks (DNNs), particularly recurrent structures like LSTMs and GRUs, further boosted performance by capturing temporal patterns, with LSTMs achieving lower prediction errors (~12.38 mg/dL RMSE) [116,117]. Recently, Transformer models, using multihead self-attention, have surpassed traditional RNNs in handling long sequences and uncertainty, delivering highly accurate multi-step glucose forecasts and opening new possibilities for closed-loop diabetes management [118,119].

Diabetes Management: Datasets for Research and Algorithm Development: Effective use of machine learning and AI in diabetes management requires high-quality datasets for model development. This section introduces four key datasets descripted in table 1[117-121]. While these datasets support the development of glucose prediction and control models, challenges remain due to variations in data quality, monitoring durations, and sampling rates. Future efforts aim to collect more diverse and comprehensive physiological data to improve model accuracy and reliability[122].

Automated Insulin Delivery Algorithms: Automated insulin delivery (AID) systems aim to ease the burden of insulin therapy in T1D by using wearable devices and smart algorithms to automatically monitor glucose and adjust insulin doses. Key approaches include: **Fuzzy Logic (FL)**, **Model Predictive Control (MPC)**, **Reinforcement Learning (RL)** presented in table 2 [123-129].

Advancing Diabetes Control: Challenges, Innovations, and Future Outlook: Despite advancements in closed-loop diabetes control, several challenges must be overcome. Some of them are as follows:

Bridging the Gap: Artificial vs. Natural Pancreas Dynamics: Current artificial pancreas (AP) systems rely mainly on glucose monitoring and insulin delivery, missing the complex hormone interactions of a natural pancreas [130,131]. Future systems may use multisensing wearable devices and dual-hormone delivery (insulin + glucagon) for better glucose regulation, with technologies like micro needles and organic electrochemical transistors improving monitoring accuracy[132,133].

Redefining Glucose Monitoring: Noninvasive Solutions: Next-generation CGMs aim to be painless and user-friendly through noninvasive methods (e.g., optical, electromagnetic), but still face challenges like physiological lag and interference factors [134,135]. Combining multimodal sensing and machine learning could boost prediction accuracy and device reliability [136].

Improving Model Training with Reliable Data: Prediction models often suffer from generalization issues due to patient variability and imbalanced datasets [134]. Future work must focus on more diverse, comprehensive data collection and apply techniques like transfer learning and advanced pre-processing to improve model robustness [137,138].

Edge-Intelligent Systems for Real-Time Diabetes Management: Deep learning models need to run efficiently on edge devices (e.g., smart watches, CGMs) for real-time, offline glucose management. Techniques like model compression, quantization, and pruning are crucial [134]. The ultimate goal is an AI-driven, wearable "cyborg pancreas" for personalized and responsive diabetes management. Edge computing also enhances data privacy by minimizing data transmission risks [137].

FutureVision: The goal is to develop intelligent, AI-powered wearable artificial pancreas systems that integrate multisensing [132], dual-hormone therapy, and personalized glucose management [134], significantly improving diabetes care and quality of life[139].

TRANSDERMAL INSULIN: Recent advancements in Needle-free transdermal jet technology have opened new avenues for insulin administration, offering a non-invasive alternative to conventional subcutaneous injections[140]. Various types of transdermal (TD) insulin delivery systems exist, but the ones that have progressed to clinical trials include TD patches, microneedle-based delivery systems, and TD insulin jet injectors. A total of 18 clinical studies have evaluated these methods.

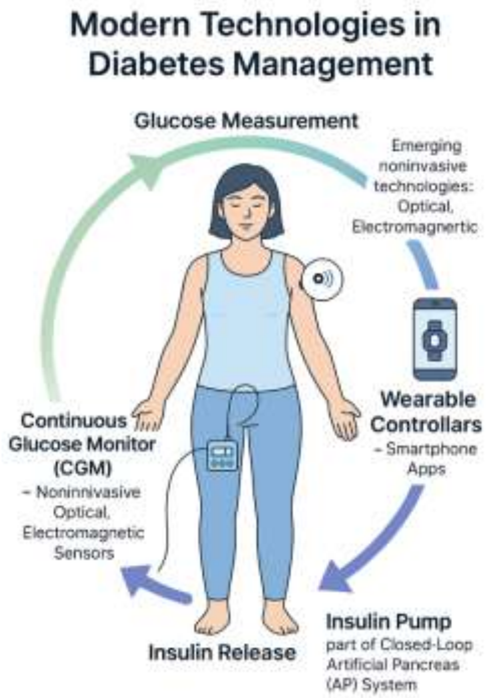

Figure 1:Empowering Diabetes Patients Through Connected Care i.e. This image illustrates how integrated technology simplifies glucose tracking and insulin delivery for improved daily management.

Table 1:Overview of Key Diabetes Datasets: A comparative summary of real-world and simulated datasets used in diabetes research, highlighting participant profiles, types of data collected, and unique features for each dataset.

Dataset	Participants	Data Collected	Special Features
OhioT1DM	12 T1D patients	CGM, insulin dosing, physiological sensors, life events	Visualization tool; extended from 6 to 12 subjects
UVA/Padova T1DMS	Simulated (virtual patients)	Simulated glucose, insulin, meals, hyper/hypoglycemia events	Realistic simulation; updated S2013 version
D1NAMO	20 healthy + 9 diabetic	CGM, insulin, 34 physiological metrics (e.g., ECG, temperature)	Most comprehensive; limited CGM duration
Shanghai T1DM/T2DM	12 T1D + 100 T2D patients	CGM, clinical profiles, labs, medications, dietary records	Real-world data from diverse patients

Table 2: Comparison of Automated Insulin Dosing Algorithms: Summary of key features, advantages, and limitations of Fuzzy Logic, Model Predictive Control, and Reinforcement Learning approaches in diabetes management systems.

Method	Key Features	Strengths	Limitations
Fuzzy Logic (FL)	Rule-based using expert-defined glucose ranges	Handles uncertainty; simple implementation	Poor personalization; limited in complex cases
Model Predictive Control (MPC)	Predicts future glucose trends and adjusts insulin proactively	Dynamic dosing optimization; responsive to real-time changes	Requires accurate models; computationally heavier
Reinforcement Learning (RL)	Learns optimal dosing policies over time from experience	Highly adaptive and personalized; handles complexity	Needs a lot of training data; longer development

High Adaptability

|

| RL

|

| MPC

|

| FL

|

|____

Low Complexity High Complexity

- **FL** → Low complexity, but low adaptability (good for simple cases).
- **MPC** → Moderate complexity, moderate-to-high adaptability (good for dynamic adjustments).
- **RL** → High complexity, very high adaptability (best for personalization but requires more data and training)[123-129].

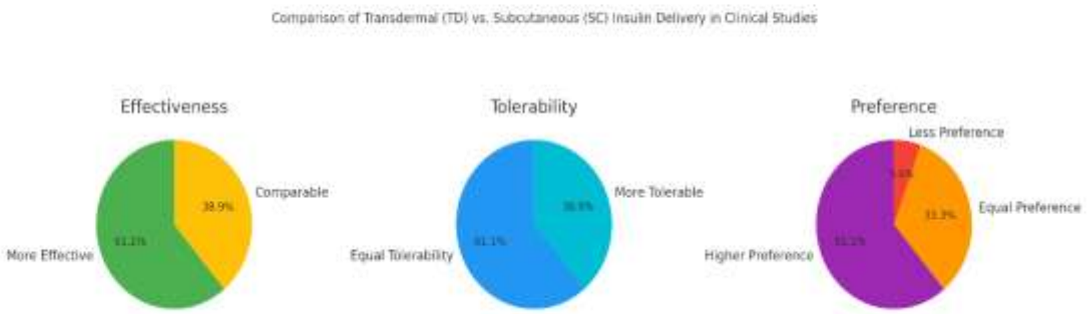

Figure 2: Results of comparable clinical studies on Transdermal insulin and traditional methods.

Table 3: Comparison of Artificial Pancreas Systems and Transdermal Insulin Pumps: An analytical overview of two advanced insulin delivery methods based on delivery routes, control mechanisms, integration, precision, and clinical suitability.

Insulin Delivery Route	Subcutaneous (via cannula/tubing)	Transdermal (via skin using microneedles, iontophoresis, etc.)
Control Type	Automated (closed-loop with CGM & algorithm)	Semi-automated or manual
Speed of Insulin Action	Fast (subcutaneous absorption)	Slower and variable
Precision & Dose Control	High – responds every 5–10 minutes using algorithms	Moderate – limited to sustained release patterns
Integration with CGM	Yes – tightly integrated for closed-loop feedback	Rarely – typically standalone systems
Device Components	CGM sensor, insulin pump, control algorithm (smartphone or dedicated)	Patch, insulin reservoir, transdermal delivery system
User Involvement	Minimal (mostly automatic)	Moderate – often needs setting or replacing patches
Best for	Type 1 diabetes patients needing tight glycemic control	Type 2 or early-stage Type 1 diabetes, needle-phobic patients
Commercial Availability	Widely available (e.g., Medtronic MiniMed 780G, Tandem Control-IQ)	In development or limited release (e.g., microneedle patches)
Challenges	Cost, complexity, frequent calibration	Slower response, limited control over sudden glucose changes

The findings indicate that TD insulin delivery is either more effective or at least comparable to traditional subcutaneous (SC) insulin administration in terms of efficacy, safety, and patient preference.visual summary of findings from 18 clinical studies comparing Transdermal (TD) insulin delivery with Subcutaneous (SC) insulin delivery is presented below in the figure 2[140]. As an innovative form of transdermal drug administration, microneedle (MN) patches offer distinct advantages such as accuracy, reduced pain, and better regulation, positioning them as a compelling alternative to traditional routes [141]. Each microneedle (MN) array consists of multiple tiny needle-like projections anchored on a base substrate, which carry therapeutic agents and penetrate the outermost skin layer to create painless microchannels for drug delivery [142,143].Upon contact with interstitial fluid, the microneedle tips swell or dissolve, enabling autonomous drug release and providing sustained delivery to the epidermis or upper dermis over an extended period[144,145].The comparison of Artificial pancreas system and transdermal insulin system is described in the below table 3[96,97,98,99,141,144,145].

Diabetes management in pediatrics:

An estimated 7.4 million individuals in the United States with diabetes rely on insulin therapy. Of these, about 1.6 million (5–10%) have type 1 diabetes (T1DM), including approximately 200,000 individuals under 20 years of age and over 1 million adults[146]. All individuals with T1DM require insulin therapy, with most using multiple daily injections (MDI)[147]. By estimation, around 5.8 million Americans with type 2 diabetes (T2DM) are also treated with insulin [148].

Tracking Insulin Pens (Stages 1-3): Tracking insulin pens use wireless communication and sensors to offer increasingly sophisticated tracking features, addressing many of the challenges associated with insulin management [153]. For instance, Novo Nordisk’s NovoPen Echo Plus (Stage 1) provides accurate retrospective dose data. There are also attachments, such as Clipsulin by Diabnext and Gocap by Common Sensing, that interface with apps to track doses, though Gocap is not yet commercially available. These devices are subject to regulatory review processes, including 510(k) exemption, clearance, or approval [154,155].

Smart Insulin Pens (Stages 4-5): Smart insulin pens mark a significant leap forward in the evolution of insulin delivery systems. By syncing with smartphones, these pens provide intelligent features that optimize insulin management [156]. The Companion Medical InPen System, FDA-cleared in 2017, is the first smart insulin pen in the U.S. Smart pens aim to address many challenges associated with insulin management, offering advanced features like weight-based therapy settings and dynamic dose titration. Though there are currently no smart insulin pens in Stage 5, the future of these devices looks promising with expectations of global growth [157]. Smart Insulin Pens (SIPs) offer two key features from Continuous Subcutaneous Insulin Infusion (CSII): personalized insulin dosing and data tracking for effective diabetes management [157]. Smart Insulin Pens (SIPs) play a significant role in enhancing therapy goals like safety, data-driven management, and improving the quality of life (QoL) for individuals on multiple daily injections (MDI). The InPen (Companion Medical, 2017), the first FDA-approved SIP in the U.S., connects via Bluetooth to a smartphone app, providing personalized insulin dose calculations and automatic data tracking. While the pen continues to function after the battery dies, it loses its smart features without the app[158]. On the other hand, the Bigfoot Unity (Bigfoot BioMedical, 2021) is a smart pen cap that integrates continuous glucose monitoring (CGM) data with healthcare provider instructions, offering insulin dose recommendations and adjustments based on both insulin and CGM data[159].These technologies aim to streamline insulin management, making it more personalized and efficient for users[158,159]. While there is some literature on SIP use, especially in adults, there is limited research, particularly regarding pediatric use [160].

SIP Data-Driven Diabetes Management and Benefits in Pediatrics:

Data-Driven Diabetes Management: The rise of telemedicine has highlighted the importance of data-driven diabetes management, with SIPs enabling remote data review and pattern management [161]. SIPs improve patient satisfaction, quality of life (QoL), and time-in-range, showing positive outcomes in adults, such as fewer missed boluses and improved clinical results at lower costs [162,163].

While data-driven benefits are established in adults, pediatric-specific results are still limited [164]. SIP technology can ease the burden on caregivers by providing automatic data tracking and reporting [165].

Benefits of SIP in Pediatrics: Ease of Use: SIPs, like InPen, are easier to set up compared to CSII (insulin pumps), requiring less education and offering step-by-step guidance. This makes them an accessible option for families[156]. Reducing Stress: SIPs can help reduce anxiety for both children and parents, especially at diagnosis, by simplifying insulin management and reducing the risk of mistakes like insulin stacking [157]. Convenience for Caregivers: SIPs allow for better tracking and reporting of data to healthcare providers, making it easier for caregivers to manage diabetes remotely [158]. Flexibility for Breaks: SIPs allow patients who typically use CSII to take breaks, such as during social events, while still having bolus calculators and pre-programmed settings [159].

Pediatric-Specific Benefits: SIPs can be customized with appealing designs and features for children, like insulin temperature tracking and alarms, helping ensure better adherence [158,159]. Additionally, using smartphone apps and widgets, parents can monitor real-time data, improving decision-making [160,161]. Challenges in Pediatrics include Adherence Issues, Design Issues, Limited Remote Monitoring, Cost and Accessibility [161].

Discussion: Diabetes management is evolving rapidly, fuelled by groundbreaking developments in pharmacological therapies, biotechnological innovations, and digital health tools. Traditional therapies, while effective in glycemic control, often fail to address the multifactorial nature of diabetes, such as weight gain, hypoglycemia risk, and long-term β-cell preservation. Technological advancements are reshaping insulin therapy. The introduction of **tirzepatide**, a dual GIP and GLP-1 receptor agonist, has been a game-changer, offering improved glycemic control along with substantial weight reduction—a dual benefit especially relevant in type 2 diabetes patients with obesity. **Orforglipron**, an oral GLP-1 receptor agonist, represents a significant step forward in patient adherence, removing the need for injectable administration. Meanwhile, Lantidra, an allogeneic pancreatic islet cell therapy, opens a potential pathway toward insulin independence in selected patients with type 1 diabetes. Although still limited by the need for immunosuppression, its success paves the way for future stem-cell or gene-based interventions. Innovations in insulin therapy are equally revolutionary. By minimizing injection burden, once-weekly insulin icodec streamlines diabetes management and promotes greater adherence. Additionally, the development of smart insulin pens, CGM devices, and the artificial pancreas integrate therapeutics with real-time glucose monitoring and automated decision-making—creating a closed-loop system that mimics physiological insulin release. Despite these advancements, challenges persist. High costs, limited accessibility in low-resource settings, regulatory hurdles, and the need for long-term safety data remain critical barriers to widespread adoption. Moreover, the integration of digital health tools requires robust patient education and infrastructure.

CONCLUSION: The current era marks a transition from conventional, one-size-fits-all approaches to more refined, targeted, and patient-friendly treatment strategies in diabetes care. Novel pharmacological agents and digital tools are not only improving metabolic outcomes but also enhancing patient satisfaction and quality of life. These novel interventions are more than incremental advancements—they are paradigm shifts that bring us closer to personalized, patient-centric diabetes care. However, realizing their full potential demands a coordinated approach involving clinicians, researchers, policy-makers, and patient communities.

Future Vision:

Looking ahead, the future of diabetology is set to be revolutionized by multifaceted advancements in science and technology. Personalized medicine will play a key role, with pharmacogenomics enabling tailored drug selection and dosing based on individual genetic and metabolic profiles. Breakthroughs in gene and cell-based therapies, including stem cell-derived solutions and gene editing tools like CRISPR-Cas9, hold the promise of curing diabetes at its root rather than merely managing it. The evolution of next-generation oral biologics will make it possible to deliver peptides and proteins, such as insulin and GLP-1 receptor agonists, without injections, thereby improving patient adherence and quality of life. In parallel, wearable and implantable biosensors will offer real-time, non-invasive monitoring of glucose levels and drug delivery, enhancing disease control. Furthermore, artificial intelligence (AI) and machine learning will be increasingly integrated into diabetes care to enable predictive analytics and real-time decision support, reducing complications and optimizing therapeutic outcomes. Central to this vision is the commitment to global equity in access, supported by low-cost manufacturing, policy-driven distribution strategies, and infrastructure development to ensure that cutting-edge therapies reach all populations. Collectively, these innovations signal a future where diabetes management becomes more proactive, personalized, and potentially curative.

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