The Crucial Roles of Different Insulin Therapies: From Short-Acting to Ultra-Long-Acting Analogs

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Abstract

Diabetes is a global disease that is characterized by ongoing high blood glucose levels due to defective insulin production and/or body insulin resistance, or a combination of both. People with type 1 diabetes and those with type 2 diabetes who experience beta-cell function deterioration need insulin therapy as their main treatment option. Modern insulin analogs follow natural body insulin patterns to provide better blood glucose management and protect patients from developing complications. The post-meal glucose regulation of rapid-acting analogs aligns with their targeted action while long-acting and ultra-long-acting formulations provide stable basal coverage with minimal glycemic fluctuations and a decrease in hypoglycemic events. The development of once-weekly basal insulin represents a novel treatment approach that enhances patient compliance by reducing the frequency of injections. The treatment of type 2 diabetes faces ongoing challenges because of hypoglycemia risks, weight fluctuations, high expenses, and limited long-term availability. This review paper aims to examine distinct types of insulin, ranging from short-acting to long-acting insulin analogs, alongside new insulin approaches, to determine their clinical applications, benefits, and drawbacks for personalized diabetes treatment. The future of diabetes treatment depends on the ongoing development of new insulin products and delivery methods, as well as affordable pricing solutions.

1. Introduction

Diabetes mellitus is a metabolic disorder characterized by elevated blood glucose resulting from defects in insulin secretion, insulin action, or both (1). Diabetes mellitus has two common forms, including type 1 diabetes and type 2 diabetes. Type 1 diabetes (T1D) results from the autoimmune destruction of pancreatic β-cells in the islets of Langerhans, leading to an absolute deficiency of insulin secretion. Without sufficient insulin, glucose cannot enter cells efficiently, causing persistent hyperglycemia. Over time, this condition disrupts the regular carbohydrate, fat, and protein metabolism and requires lifelong exogenous insulin therapy for glucose regulation (1). Type 2 diabetes (T2D) develops when peripheral tissues, primarily skeletal muscle, the liver, and adipose tissue, become insulin resistant. In the early stages, pancreatic β-cells compensate by increasing insulin secretion. However, chronic metabolic stress eventually leads to β-cell dysfunction and decreased insulin production. The combination of insulin resistance and relative insulin deficiency leads to elevated blood glucose levels (hyperglycemia). T2D is spreading rapidly worldwide. There are more than 530 million adults living with it now, and it is expected to reach 783 million by 2045 (2). Most of these cases are T2D, and the increase is driven by factors such as obesity, poor eating habits, and insufficient physical activity (3). If it is not managed correctly, it can cause serious health problems and significantly burden healthcare systems (2). Prolonged hyperglycemia damages microvascular and macrovascular systems, contributing to complications such as retinopathy, nephropathy,

neuropathy, cardiovascular disease, and stroke (1,4). Therefore, it is essential to treat them effectively and safely.

Insulin therapies are a key component of diabetes management for individuals with T1D and T2D. Lifestyle changes and anti-diabetic medications can also be effective in managing T2D, alone or in combination with insulin (4). In contrast, insulin therapies remain essential for patients with T1D and those with progressive beta-cell dysfunction. Thus, insulin therapies are necessary for treating diabetes in clinical practice. Early and steady insulin therapy is an integral part of managing T2D because it mimics the body's regular insulin release. In healthy individuals, insulin is available in two forms. Basal insulin is the steady amount that maintains normal blood glucose levels between meals. Bolus insulin is the extra burst of insulin that comes after eating to prevent blood glucose from rising too high (5). Basal insulin primarily prevents the liver from producing excessive sugar. Bolus insulin helps muscle and fat cells use sugar for energy (4). The UK Prospective Diabetes Study demonstrated that maintaining well-controlled blood glucose levels with insulin reduces the risk of small-vessel damage in the eyes, kidneys, and nerves (6). Daily basal shots, such as glargine and degludec, help keep sugar steady throughout the day, but making them every day can be challenging for some people (1).

Newer weekly insulins (e.g., icodec) make this easier. Studies have found that weekly icodec is approximately as effective as daily insulin in controlling blood glucose levels and safety (7,8). Having fewer injections can also help people stay on their treatment longer and feel more comfortable with it. However, optimizing insulin therapies remains limited by several limitations, including the risk of hypoglycemia, weight gain, and patient adherence issues (9). Therefore, it is vital to understand the distinct roles of various insulin analogs, including short- and long-acting, to tailor regimens that closely mimic physiological insulin secretion (10). This review paper examines and compares multiple insulin analogs, focusing on their short-term effects for clinical use in the management of T1D and T2D. It also evaluates how these various strategies influence glycemic control, patient adherence, quality of life, and safety outcomes, while optimizing their potential in individualized diabetes care.

2. Physiological Role of Insulin

The pancreas is a crucial endocrine organ that secretes insulin and glucagon. Insulin is a peptide hormone that reduces blood glucose levels (3). Insulin is usually secreted from beta cells in the pancreas after a meal to decrease blood glucose levels (3). In this way, insulin facilitates the entry of glucose into cells for energy production, and excess glucose is stored as glycogen in the liver and muscles for future use (11). The hormone also regulates fat metabolism by slowing the breakdown of triglycerides in adipose tissue and promoting the lipid storage for later energy use (12). Thus, the body maintains blood glucose within safe limits through this process (1). Figure 1 summarizes the action of insulin on metabolic tissues in healthy individuals. Glucagon is another hormone released by alpha cells in the pancreas that acts in opposition to insulin. The liver releases sugar into the bloodstream via glucagon to provide glucose for an extended period of fasting (11). The body uses insulin to lower blood glucose levels, whereas glucagon raises them. The two hormones work together to maintain a balance, providing a continuous energy supply to the body.

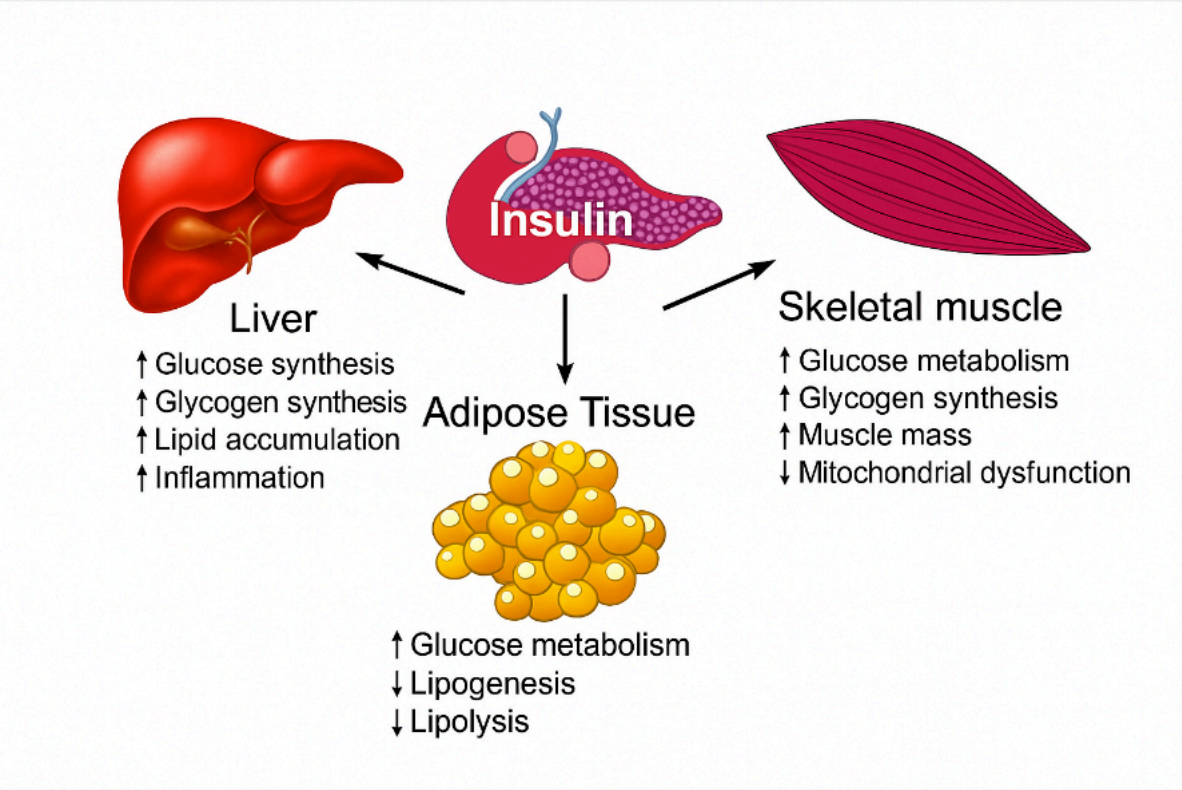

Figure 1. Physiological role of insulin. This figure highlights that reduced insulin action in diabetes decreases glucose uptake and glycogen synthesis while increasing fat breakdown, resulting in sustained hyperglycemia. This figure was created on BioRender.com.

2.1 Insulin in T1D

The immune system of people with T1D attacks and destroys pancreatic β-cells, which produce insulin. This autoimmune destruction of pancreatic β-cells results in absolute insulin deficiency, meaning that the pancreas can no longer produce sufficient insulin to regulate blood glucose levels (1). The body fails to transport glucose to muscle, liver cells, and adipose tissue for energy or storage (1).

Patients with T1D need to take exogenous insulin for their entire lives because their bodies stop producing insulin naturally. The American Diabetes Association explains that insulin treatment mimics natural insulin patterns with two types of doses: basal insulin, which regulates blood glucose between meals, and bolus insulin, which handles the rise in blood glucose after eating. The two components require exact proportions to prevent both high blood glucose and low blood glucose levels and minimize the risk of developing microvascular and macrovascular complications (6).

2.2 Insulin in T2D

The physiological balance between insulin and glucagon becomes progressively impaired during the development of T2D, particularly in this condition (3). Peripheral tissues gradually

develop resistance to insulin signaling, prompting β-cells to increase insulin secretion to maintain glucose homeostasis (4). However, this compensatory mechanism eventually fails as β-cell function declines, resulting in sustained hyperglycemia. The resulting elevation in blood glucose deprives cells of the energy they need, and over time, it induces widespread vascular and organ damage. Chronic hyperglycemia contributes to complications, including neuropathy, nephropathy, retinopathy, and cardiovascular disease (2,4). The coordinated action of insulin and glucagon is therefore crucial to preserving metabolic health and preventing these pathological outcomes.

3. Essential Role of Insulin Therapies for the Treatment of T2D

Insulin therapies remain the cornerstone of treatment for both T1D and T2D. In T1D, exogenous insulin administration is vital for survival and metabolic regulation. However, patients with T2D often experience progressive beta-cell dysfunction following a period of insulin resistance, necessitating insulin therapy when anti-diabetic agents are no longer sufficient to control glucose levels (4).

Recent insulin therapies range from rapid, regular/short-acting, intermediate-acting, long-acting, and ultra-long-acting analogs (13). The relative onset, peak, and duration of action for these insulin analogs are illustrated in **Figure 2**, which shows how their activity profiles differ over time. They allow for flexible and physiologic replacement strategies that closely mimic endogenous insulin secretion patterns (10). Significantly, continuous insulin infusion and hybrid closed-loop systems improve glycemic precision and reduce the risk of hypoglycemia (14). Thus, effective insulin therapies help prevent long-term diabetes-associated complications and contribute to comprehensive diabetes management. **Table 1** summarizes the pharmacokinetic differences among rapid-acting, short-acting, intermediate-acting, long-acting, ultra-long-acting, and once-weekly insulin formulations, including their onset, peak activity, duration, and underlying mechanisms of absorption (7,13,15–17).

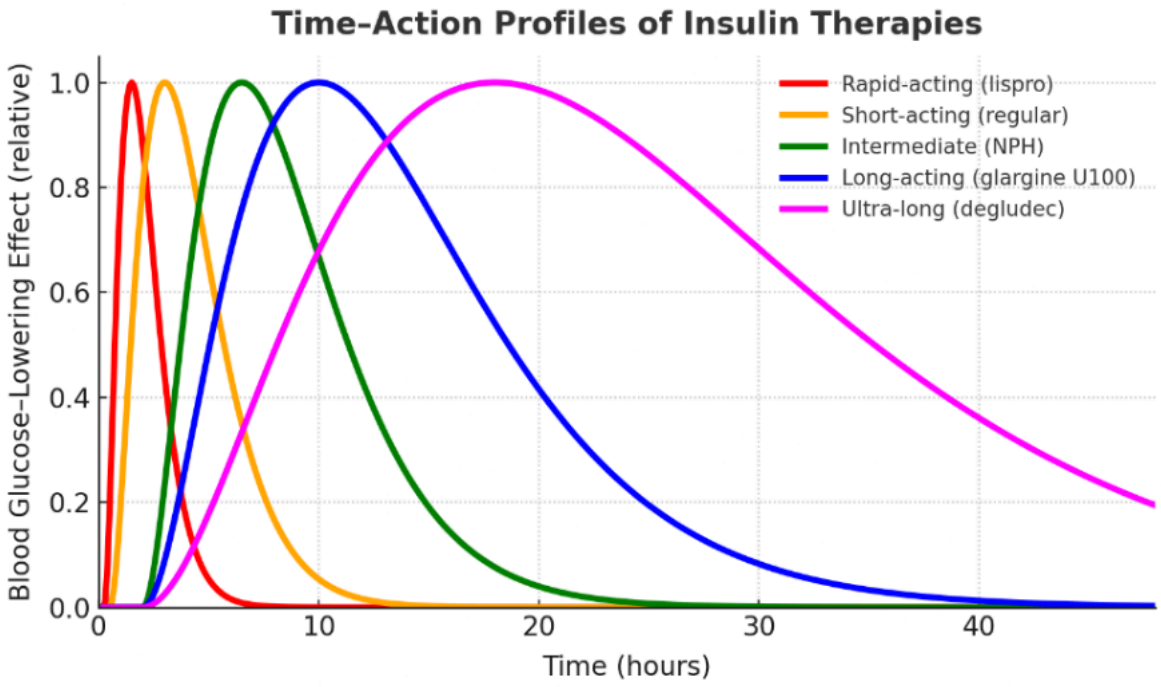

Figure 2. Time–action profiles of insulin therapies, ranging between rapid-acting and ultra-long-acting analogs. This figure shows relative blood glucose–lowering effects of insulin types over time. The y-axis represents the magnitude of blood glucose–lowering effect (insulin activity level), while the x-axis shows time after injection (hours). Rapid-acting (red) acts within ~15 min and lasts 3–5 h; short-acting (orange) begins ~0.5 h, peaks 2–4 h, lasts up to 8 h; intermediate (green) starts ~2 h, peaks ~6–8 h, lasts ~16 h; long-acting (blue) maintains ~24 h; ultra-long (magenta) exceeds 42 h with minimal peak (7,10,15–17).

Table 1. Comparison of insulin analog types by onset, peak, and duration of action.

Type	Examples	Onset	Peak	Duration	Structure	Advantages
Rapid-Acting Insulin	Lispro, Aspart, Glulisine	10–20 minutes	1–2 hours	3–5 hours	Amino-acid modifications prevent hexamer formation, remain monomers	Precise mealtime control; reduced post-meal spikes
Short-Acting (Regular) Insulin	Regular (Humulin R, Novolin R)	30–45 minutes	2–4 hours	Up to 8 hours	Forms hexamers → slower absorption	Must be injected 30–45 min before meals; risk of delayed hypoglycemia
Intermediate-Acting Insulin	NPH	1–2 hours	4–12 hours	~16 hours	Protamine-bound insulin forms crystals → slow dissolution	Used in split-mixed regimens; more variable absorption and nocturnal hypoglycemia
Long-Acting Insulin	Glargine	~1 hour	Minimal peak	~24 hours	Forms micro-precipitates in subcutaneous tissue → steady release	Provides stable basal insulin; once-daily dosing
Ultra-Long-Acting Insulin	Degludec	~1 hour	Minimal peak	~42 hours	Hexamer chains + albumin binding → slow release	Very low hypoglycemia risk; flexible dosing window
Once-Weekly Basal Insulin	Icodec	Slow onset	Minimal peak	7 days	Strong albumin-binding + sustained-release structure	Improves adherence by reducing injection burden

3.1 Rapid-Acting Insulin Therapies

The design of rapid-acting insulins enables them to start working immediately after injection through modifications to the β-chain amino acids that prevent hexamer formation. The molecules remain monomers and enter the bloodstream immediately after subcutaneous administration. The fast-acting insulin group includes insulin, lispro, aspart, and glulisine, which start working within 10–20 minutes and reach their peak effect after 1–2 hours (13). The analogs are absorbed into the body, where they bind to insulin receptors in muscle, liver, and adipose tissue, enhancing glucose uptake and glycogen synthesis while blocking glucose release from the liver (11).

Rapid-acting insulins help patients with T1D and T2D achieve better HbA1c results, and better control of postprandial blood glucose levels is achieved through their use in basal-bolus treatment plans. The drugs create a moderate risk of hypoglycemia when patients fail to eat their meals or consume excessive amounts of their medication. The brief treatment period of 3–5 hours allow doctors to adjust medication schedules, as patients can receive their injections immediately before meals, thereby helping to prevent hypoglycemia after meals (13). Rapid-acting analogs have demonstrated better time-in-range results than regular insulin when used to treat both T1D and T2D (15).

3.2 Regular or Short-Acting Insulin Analogs

Human insulins, whether regular or short-acting, form hexamers after subcutaneous injection, resulting in delayed absorption. Due to their molecular structure, they take

approximately 30–45 minutes to begin acting and reach their peak around 2–4 hours, with a total duration of up to 8 hours (16). Examples include Humulin R and Novolin R. These insulins produce insulin release patterns that are less similar to endogenous insulin than those of rapid-acting analogs. However, they still help control blood glucose and HbA1c levels when taken correctly before meals. The main drawback of this treatment is its restricted dosing options because patients need to administer the medication through injection 30–45 minutes before their meals, which could make it harder to follow the treatment plan. Short-acting insulins create a risk for delayed hypoglycemia, which becomes more likely when people have irregular eating patterns. Regular insulin is as adequate as rapid-acting analogs in T2D clinical research; however, T1D patients achieve superior postprandial control and greater satisfaction with analogs (9).

3.3 Intermediate-Acting Insulin Analogs

The combination of insulin with protamine and zinc produces intermediate-acting insulin crystals, which dissolve at a steady rate after subcutaneous injection. The modified formulation causes insulin to be absorbed at a reduced rate, resulting in delayed drug absorption that begins between 1 and 2 hours after administration and continues for 16 hours (17). Common preparations include NPH (Neutral Protamine Hagedorn) insulin.

The different absorption rates of these insulins between meals and at night result in irregular blood glucose spikes and nighttime episodes of hlow blood glucose levels. The combination of intermediate-acting insulin with short- or rapid-acting formulations in split-mixed regimens remains effective for patients with T1D and T2D, despite these limitations. The clinical data indicate that patients experience significant reductions in HbA1c during treatment, but their glucose levels become more unpredictable than those of patients receiving long-acting analogs (17,18). The twice-daily dosing schedule of these medications provides moderate flexibility, but patients need to maintain regular dosing times for optimal control (9).

3.4 Long-Acting Insulin Analogs

The chemical alteration of long-acting insulins produces a steady 24-hour basal glucose control. Long-acting insulins provide steady 24-hour basal glucose control through distinct release mechanisms; glargine forms micro-precipitates that remain in the subcutaneous tissue, while degludec forms multi-hexamers that slowly release insulin monomers into circulation (10). The extended absorption pattern and flat concentration curve of these substances result from their structural variations which prevent significant blood glucose spikes (10).

Long-acting insulins lead to better HbA1c results, improved fasting glucose levels, and better time-in-range measurements, while reducing the risk of nocturnal hypoglycemia compared to intermediate-acting insulin (18). The drug maintains a steady release profile, enabling doctors to prescribe it as a single daily dose, which enhances patient compliance and treatment satisfaction (10). Both T1D and T2D patients benefit from improved blood glucose stability without an increased risk of hypoglycemia (10,18). For long-acting insulins, subcutaneous administration is more common than oral administration, as it avoids enzyme degradation of the compounds before they reach the bloodstream (19).

3.5 Ultra Long-Acting Insulin Analogs

Ultra-long-acting insulins provide extended basal control for more than 24 hours, allowing patients to choose their injection time and minimize the effects of missed doses. The multi-hexamer structure of insulin degludec, together with its strong albumin-binding properties, enables extended release of the medication for 42 hours (20). The system generates stable plasma insulin levels that remain steady throughout the day with minimal changes from one day to the next (21). Studies show that ultra-long-acting insulins achieve HbA1c levels comparable to those of long-acting analogs while reducing the frequency of nocturnal and severe hypoglycemic events (7,20). The more extended treatment period helps patients stick to their medication plan, which leads to better drug compliance and decreased mental stress from daily injections. These benefits are consistent in both T1D and T2D populations (7,22). The current treatment of diabetes combines ultra-long-acting insulins with GLP-1 receptor agonists to improve blood glucose control by reducing insulin requirements (23).

4. Novel Therapeutic Strategies: Combining Insulin with Other Diabetes Treatments

While conventional insulin regimens remain effective for many patients, recent advances focus on combining insulin with complementary agents to improve long-term outcomes (3). The new treatment methods focus on controlling blood glucose levels through multiple mechanisms (5). The treatment approach maintains stable glucose levels while minimizing daily insulin requirements. The combination of these treatments helps patients avoid gaining weight and experiencing hypoglycemic episodes (5).

4.1 Insulin and GLP-1 Receptor Agonists

Several ways using insulin in combination with GLP-1 receptor agonists (e.g., liraglutide, lixisenatide, semaglutide) enhance blood glucose control (22). These medications enable the pancreas to release insulin only in response to elevated blood glucose levels by slowing the rate at which food exits the stomach. By doing this, post-meal glucose rises. The combination of insulin analogs such as glargine with lixisenatide and degludec with liraglutide has been shown to reduce A1C levels and decrease the occurrence of hypoglycemic events (22,23).

4.2 Insulin and SGLT2 Inhibitors

Empagliflozin and dapagliflozin are examples of SGLT2 inhibitors that work in the kidneys to prevent glucose reabsorption (4). Instead, excess sugar is eliminated through urine. These medications lower A1C without requiring larger insulin dosages when used in combination with insulin (4). The treatment approach should also protect the kidneys and heart (4). Doctors still follow patients cautiously since reducing insulin too soon might enhance the risk of dehydration or ketoacidosis (4).

4.3 Insulin and Metformin

Metformin is usually the first drug prescribed for Type 2 Diabetes. The treatment method works through two mechanisms that decrease liver glucose output and enhance insulin responsiveness in targeted tissues (4). When added to insulin therapy, metformin improves

overall blood glucose control and can reduce the daily insulin requirement. It also helps prevent some of the weight gain that can come with insulin use (6).

4.4 Future Directions

Multiple obstacles exist for future insulin therapies that seek to duplicate natural glucose regulation. The automatic insulin delivery system, known as “closed-loop” artificial pancreas, operates more effectively through enhanced sensor precision and proper patient education (14). Future systems will address these problems through the implementation of dependable sensors and self-calibrating technology, as well as user-friendly operating systems.

The combination of insulin with GLP-1 receptor agonists leads to better blood glucose management while decreasing the amount of insulin patients need to take (22,23). The current treatment approaches face two major obstacles: they produce adverse effects and require complex administration procedures. The development of single-injection combination pens with enhanced dose-guidance tools presents a solution to overcome existing treatment challenges.

Glucose-sensitive "smart" insulins are another alternative solution that activates during blood glucose increases; however, researchers need to prove their safety and reliable glucose response (14). Continued molecular refinement and standardized clinical testing are necessary to ensure stability and safe use over time.

The other main obstacles are associated with high costs and restricted access to weekly basal insulin and automated delivery systems (2,3). Medical breakthroughs will reach patients across every socioeconomic level, thanks to the expansion of biosimilars, insurance-backed coverage systems, and global pricing strategies, which will make them more accessible.

5. Conclusion

Insulin remains the cornerstone of diabetes treatment due to its essential role in maintaining glucose homeostasis and preventing metabolic complications. Both short- and long-acting insulin analogues provide significant therapeutic benefits by allowing individualized treatment regimens that closely mimic physiological insulin secretion. Rapid-acting analogues enable precise mealtime glucose control, while long- and ultra-long-acting formulations offer sustained basal coverage, reducing glycemic variability, and the risk of hypoglycemia. Recent progress in ultra-long-acting and once-weekly insulin therapies represents a significant advancement in diabetes management. These formulations improve patient adherence, comfort, and overall quality of life by reducing the frequency of injections without compromising safety or efficacy. However, continued research remains necessary to evaluate the long-term outcomes, affordability, and accessibility of these innovations across diverse populations. Future studies must focus on integrating these therapies into broader diabetes care frameworks that emphasize both clinical effectiveness and equitable global access.

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