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Emerging Therapeutic Approaches for Type 2 Diabetes Mellitus: A Comprehensive Review

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Abstract

Type 2 diabetes mellitus (T2DM) is a heterogeneous, progressive metabolic disorder characterized by insulin resistance, inadequate pancreatic β-cell compensation and chronic hyperglycaemia. Its treatment landscape has shifted from a predominantly glucose-centred model toward therapies that also modify body weight and reduce cardiovascular, kidney and liver risk. This narrative review examines established therapies that have reshaped contemporary care and emerging approaches likely to influence the next generation of T2DM management. Particular attention is given to incretin-based medicines, including dual glucose-dependent insulinotropic polypeptide/glucagon-like peptide-1 (GLP-1) receptor agonism and investigational triple agonism; oral small-molecule GLP-1 receptor agonists; amylin-based combinations; sodium–glucose cotransporter-2 (SGLT2) inhibitors; non-steroidal mineralocorticoid receptor antagonism; metabolic surgery; precision medicine; β-cell preservation and regeneration; and microbiome-directed interventions. Clinical trial evidence supports substantial glucose and weight reductions with tirzepatide and promising early efficacy for retatrutide and oral GLP-1 candidates. Semaglutide has also demonstrated kidney outcome benefit in people with T2DM and chronic kidney disease. Nevertheless, emerging agents differ markedly in development stage, evidence quality, safety profile, cost and regulatory status. Regenerative, microbiome and precision approaches remain investigational or adjunctive rather than established replacements for evidence-based pharmacotherapy. The review concludes that future care will likely combine potent metabolic medicines with cardiorenal protection, individualized treatment selection, accessible delivery systems and long-term lifestyle support. The central challenge is to translate impressive trial efficacy into durable, safe and equitable outcomes in routine practice.

Keywords:

Keywords: retatrutide, amylin, SGLT2 inhibitor, cardiorenal protection, precision medicine, β-cell regeneration; metabolic surgery.

1. Introduction

T2DM is a major global health challenge because its prevalence, duration and associated complications continue to increase. The disease is not simply a disorder of elevated blood glucose. It involves interacting abnormalities in skeletal-muscle and hepatic insulin action, adipose-tissue biology, pancreatic β-cell function, renal glucose handling, gut hormone signalling, appetite regulation and the cardiovascular system. Consequently, glucose lowering alone is an incomplete measure of therapeutic success. Contemporary treatment increasingly seeks to reduce microvascular and macrovascular complications, preserve kidney function, manage obesity and address associated metabolic liver disease (American Diabetes Association Professional Practice Committee, 2025). For decades, metformin, sulfonylureas, thiazolidinediones and insulin formed the principal pharmacological framework. These medicines remain useful, but their limitations including hypoglycaemia, weight gain, gastrointestinal intolerance, fluid retention or treatment burden have encouraged development of agents with complementary mechanisms. Incretin-based medicines and SGLT2 inhibitors have been particularly influential because benefits extend beyond HbA1c reduction. Their clinical effects have prompted a broader definition of diabetes therapy: the best treatment is not necessarily the agent that produces the largest short-term fall in glucose, but the regimen that best addresses an individual's glycaemic, weight, cardiovascular, kidney, hepatic and safety priorities.

2. Pathophysiological basis for innovation

Insulin resistance and β-cell dysfunction are central to T2DM, but their relative contribution varies between individuals and across disease duration. Excess hepatic glucose production contributes to fasting hyperglycaemia, while impaired muscle glucose uptake contributes to postprandial and overall glucose elevation. Adipose-tissue dysfunction increases free-fatty-acid flux and inflammatory signalling. Progressive β-cell dysfunction limits insulin secretion as metabolic demand rises. The kidney contributes by reabsorbing filtered glucose, and the intestine and brain regulate nutrient sensing, satiety and energy balance. The incretin hormones GLP-1 and GIP amplify glucose-dependent insulin secretion. GLP-1 also slows gastric emptying, suppresses inappropriate glucagon secretion and reduces appetite. Amylin, co-secreted with insulin, contributes to satiety and postprandial glucose regulation. Glucagon has complex actions: it can increase hepatic glucose output but may also increase energy expenditure when combined with other gut-hormone pathways. SGLT2 inhibition lowers renal glucose reabsorption, producing urinary glucose excretion and haemodynamic effects. These mechanisms explain why multi-target medicines may influence glucose, body weight and cardiometabolic risk simultaneously (Drucker, 2025; Bailey, 2025).

3. Review methodology

A narrative literature-review approach was used to integrate clinical and translational evidence relevant to emerging T2DM therapeutics. The source framework prioritized peer-reviewed randomized controlled trials, cardiovascular and kidney outcome trials, systematic reviews, high-quality mechanistic reviews, and professional clinical guidance. Searches were framed around T2DM, emerging therapy, incretin co-agonist, triple agonist, oral GLP-1, amylin, SGLT2, finerenone, β-cell regeneration, precision medicine, microbiome and metabolic surgery. PubMed-indexed records, journal websites and guideline publications were used to identify relevant literature. Landmark trials were retained where they provide the clinical foundation for newer approaches. Evidence was summarized qualitatively rather than pooled statistically. No formal risk-of-bias assessment, PRISMA flow diagram or quantitative meta-analysis was undertaken; therefore, this article should be interpreted as a narrative review rather than a systematic review. Particular care was taken to distinguish approved medicines from investigational agents and to avoid treating sponsor-reported preliminary findings as definitive clinical outcomes. Trial phase, population, comparator, follow-up duration and endpoint type are important when comparing agents. Where a therapy has only early-phase evidence, this limitation is explicitly stated. Clinical recommendations remain guided by local regulatory approval and professional guidelines, not by investigational results.

4. Evolution from glucose-centric to outcome-based treatment

The therapeutic goal in T2DM has expanded beyond HbA1c. Modern care considers atherosclerotic cardiovascular disease (ASCVD), heart failure, chronic kidney disease (CKD), obesity, metabolic dysfunction-associated steatotic liver disease and hypoglycaemia risk. The American Diabetes Association recommends person-centred selection of glucose-lowering medicines, incorporating comorbidities, weight goals, adverse effects, cost, access and patient preferences. For people with established or high-risk ASCVD, heart failure or CKD, agents with demonstrated cardiovascular or kidney benefit should be considered irrespective of baseline HbA1c or metformin use (American Diabetes Association Professional Practice Committee, 2025). This framework changes the meaning of therapeutic innovation. A new medicine should be evaluated not only by its glucose-lowering potency but also by its effects on weight, cardiovascular events, kidney disease progression, liver disease, quality of life and treatment burden. Long-term outcomes are especially important because T2DM is a chronic condition requiring sustained treatment. A therapy that produces striking short-term weight loss but has poor tolerability, high cost or uncertain long-term safety may have limited population-level impact. Similarly, a modest glucose-lowering effect may still be valuable if it reduces heart-failure hospitalization or slows CKD progression.

5. Incretin biology and GLP-1 receptor agonism

GLP-1 receptor agonists (GLP-1 RAs) reproduce selected actions of endogenous GLP-1. They enhance insulin secretion in a glucose-dependent manner, suppress glucagon when glucose is elevated, delay gastric emptying to varying degrees and reduce appetite. These effects lower glucose while generally producing weight loss and relatively little intrinsic hypoglycaemia when not combined with insulin or insulin secretagogues. Semaglutide and other GLP-1 RAs have demonstrated cardiovascular benefits in selected high-risk populations, while the FLOW trial established an

important kidney-outcome signal for semaglutide in T2DM with CKD (Perkovic et al., 2024). Despite their success, GLP-1 RAs do not meet every clinical need. Gastrointestinal adverse effects, injectable administration for many formulations, treatment cost, supply constraints and variable individual response can limit use. Weight regain may occur after treatment discontinuation, highlighting the chronic nature of obesity biology. Newer approaches therefore seek greater efficacy, more convenient oral delivery, longer dosing intervals or complementary receptor activity. It is important to distinguish an established GLP-1 RA from a new candidate: the class is clinically validated, whereas the performance and safety of next-generation compounds must be established separately.

6. Dual GLP-1 receptor agonism: tirzepatide

Tirzepatide is a once-weekly peptide that activates both GIP and GLP-1 receptors. Its development represents a major advance in multi-incretin pharmacology. The dual mechanism is intended to combine glucose-dependent insulinotropic effects with appetite and weight regulation. In the SURPASS clinical programme, tirzepatide produced substantial HbA1c reductions and weight loss compared with placebo and several active comparators. In SURPASS-4, it was compared with insulin glargine in adults with T2DM and increased cardiovascular risk; the trial contributed important cardiovascular safety information (Del Prato et al., 2021). The clinical relevance of tirzepatide is not limited to glycaemia. Weight reduction can improve insulin resistance, blood pressure, lipid profile and hepatic steatosis. However, nausea, diarrhoea, vomiting and constipation are common, particularly during dose escalation. As with other incretin therapies, gradual titration and assessment of tolerability are important. Hypoglycaemia risk rises when combined with insulin or sulfonylureas, so background treatment may need adjustment. Tirzepatide is an established therapeutic option in jurisdictions where approved; it should not be described as an investigational drug. Its longer-term cardiovascular, renal and real-world effectiveness evidence continues to evolve.

7. Triple agonism: retatrutide

Retatrutide is an investigational peptide designed to activate GIP, GLP-1 and glucagon receptors. The rationale is to integrate incretin-mediated insulin secretion and appetite suppression with glucagon-associated effects on energy expenditure and hepatic metabolism. In a phase II randomized trial involving adults with T2DM, retatrutide improved glycaemic control and body weight compared with placebo and an active comparator (Rosenstock et al., 2023). These results generated substantial interest in triple-agonist pharmacology. However, retatrutide remains distinct from approved standard therapy, and phase II findings cannot establish long-term cardiovascular benefit, rare adverse-event risk or durable effectiveness. Gastrointestinal adverse effects are relevant, as are potential effects associated with glucagon receptor activation, including heart rate changes and altered hepatic glucose regulation. Dose selection and receptor balance are critical: greater pharmacological activity does not automatically produce a better therapeutic index. Ongoing later-phase trials must determine whether the observed efficacy translates into clinically meaningful improvements in diabetes complications and whether benefits outweigh tolerability, safety and cost concerns.

8. Other incretin co-agonists and pipeline diversity

The pipeline includes compounds that combine GLP-1 activity with glucagon receptor agonism, GIP receptor modulation or additional metabolic targets. Examples discussed in contemporary reviews include survodutide, mazdutide and maridebart cafraglutide. Their mechanisms are not interchangeable. GLP-1/glucagon co-agonism aims to balance appetite reduction and glucose-dependent insulin secretion with energy expenditure and hepatic effects. Other compounds explore GIP agonism or antagonism in combination with GLP-1 signalling. The biological rationale is to address multiple components of obesity and T2DM simultaneously (Bailey, 2025; Drucker, 2025, 2026). The development landscape is dynamic, and candidate names, trial phases and indications may change. A compound demonstrating weight loss in obesity does not necessarily have established efficacy in T2DM. Diabetes-specific endpoints, background medications, baseline HbA1c, duration and safety outcomes must be examined separately. The possibility of greater weight loss raises additional questions about lean-mass preservation, nutritional adequacy, gallbladder events, gastrointestinal tolerability and long-term adherence. Future comparative trials should establish whether multi-agonists provide clinically meaningful advantages over existing high-efficacy therapies rather than simply demonstrating superiority to placebo.

9. Oral small-molecule GLP-1 receptor agonists

Oral delivery is a major pharmaceutical objective because it may improve convenience, reduce injection barriers and expand treatment access. Peptide drugs are often difficult to administer orally because of enzymatic degradation and limited intestinal permeability. Small-molecule GLP-1 receptor agonists are designed to overcome some of these limitations. Orforglipron is an investigational oral non-peptide GLP-1 receptor agonist evaluated in clinical studies of T2DM and obesity. A phase II study in adults with T2DM reported improvements in glycaemic measures and body weight, supporting further development (Pratley et al., 2023). Oral small molecules may offer manufacturing and formulation advantages compared with complex peptide products, but these benefits must be demonstrated in practice. Important considerations include dose-response, food effects, drug interactions, hepatic metabolism, adherence, gastrointestinal tolerability and long-term safety. Oral administration alone does not guarantee affordability or access. Moreover, an oral candidate should be compared with established oral agents and oral semaglutide where relevant. Regulatory approval requires adequate evidence from large, well-controlled trials, including cardiovascular safety where required. Until then, these compounds should be regarded as investigational rather than recommended routine therapy.

10. Amylin-based therapeutics and combination strategies

Amylin is a pancreatic hormone co-secreted with insulin that contributes to satiation, gastric emptying and postprandial glucose regulation. Pramlintide, an amylin analogue, has been used as adjunctive therapy in selected insulin-treated patients, but its injection burden and risk of hypoglycaemia when insulin is not adjusted limit broad use. Newer amylin analogues and combination strategies seek longer duration of action and complementary appetite effects. Cagrilintide combined with semaglutide (CagriSema) is one example of combining amylin and GLP-1 pathways. Amycretin/zenagamtide has been developed as a unimolecular GLP-1 and amylin receptor agonist; a phase II trial reported clinically meaningful HbA1c reductions in adults with T2DM (Mora et al., 2026). These approaches are promising but require careful interpretation. A combination that produces greater weight reduction may also increase gastrointestinal adverse events or treatment discontinuation. Long-term effects on nutritional status, lean body mass, gallbladder disease and cardiovascular outcomes remain important research questions. The availability and regulatory status of individual amylin-based candidates vary by jurisdiction and date. They should not be confused with approved, established diabetes medicines unless a specific product has received local authorization.

11. SGLT2 inhibitors: from glucose lowering to organ protection

SGLT2 inhibitors reduce glucose reabsorption in the proximal renal tubule, increasing urinary glucose excretion. Their glucose-lowering effect depends partly on kidney function, but cardiorenal benefits extend beyond HbA1c reduction. Proposed mechanisms include altered tubuloglomerular feedback, reduced intraglomerular pressure, natriuresis, changes in plasma volume and improved renal and cardiac energetics. Mechanistic reviews describe how these effects may contribute to lower heart-failure and kidney-disease risk (Vallon, 2024). SGLT2 inhibitors are now foundational for many people with T2DM and heart failure or CKD. Their benefits are not dependent solely on glucose lowering, and professional guidance recommends them for relevant comorbidities irrespective of HbA1c. Adverse effects include genital mycotic infections, volume depletion and rare euglycaemic diabetic ketoacidosis. Temporary withholding may be appropriate during prolonged fasting, severe acute illness or around surgery according to clinical protocols. Patients require education about hydration, sick-day rules and symptoms of ketoacidosis. The class illustrates a broader therapeutic principle: diabetes drugs can protect organs through mechanisms partly independent of their effects on blood glucose.

12. Kidney-protective therapy: GLP-1 and mineralocorticoid pathways

The FLOW trial evaluated semaglutide in people with T2DM and CKD. Semaglutide reduced the risk of the trial's primary kidney and cardiovascular composite outcome compared with placebo, adding dedicated kidney-outcome evidence to the broader GLP-1 literature (Perkovic et al., 2024). This supports a more integrated approach in which glucose-lowering therapy is selected partly for renal protection. The magnitude of benefit and suitability of treatment depend on patient characteristics, background therapy and local guidance. Finerenone, a non-steroidal mineralocorticoid receptor antagonist, is not a glucose-lowering medicine but is an important emerging component of comprehensive metabolic-kidney care. In the FIDELITY pooled

analysis of FIDELIO-DKD and FIGARO-DKD, finerenone reduced cardiovascular and kidney composite outcomes in people with T2DM and CKD (Agarwal et al., 2022). Hyperkalaemia is a key safety concern, requiring appropriate patient selection and potassium monitoring. Combining SGLT2 inhibitors, GLP-1 RAs and finerenone may provide complementary protection, but sequencing and monitoring should be individualized. These treatments demonstrate why a modern review of T2DM therapeutics must include organ-protective agents even when their primary indication is not glycaemic control.

13. Fixed-dose combinations and treatment simplification

Combination therapy can improve the probability of reaching individualized glycaemic targets, particularly when baseline HbA1c is substantially above target. Fixed-dose combinations may reduce pill burden and simplify administration, potentially improving adherence. Established combinations include metformin with DPP-4 inhibitors, SGLT2 inhibitors or thiazolidinediones, while basal insulin,GLP-1 RA combinations offer a way to combine complementary mechanisms. The ADA recommends reassessing treatment regularly and avoiding therapeutic inertia; it also advises against combining a DPP-4 inhibitor with a GLP-1 RA because additional glucose lowering is not expected (American Diabetes Association Professional Practice Committee, 2025). Future combination strategies may include oral small molecules with complementary pathways, incretin plus amylin combinations, and cardiorenal regimens that address distinct risk domains. The challenge is to demonstrate that combinations improve meaningful outcomes without excessive complexity, cost or adverse effects. Pharmacists can contribute through medication reconciliation, adherence support, injection education, hypoglycaemia prevention and identification of drug interactions. Combination therapy should not be interpreted as indiscriminate polypharmacy: each component should have a clear purpose and be reviewed as the patient's clinical status changes.

14. Insulin innovation and glucose-responsive delivery

Insulin remains essential when endogenous insulin secretion becomes insufficient or when severe hyperglycaemia, catabolism or symptomatic glucose toxicity is present. Innovation includes longer-acting basal insulins, ultra-rapid formulations, concentrated preparations, connected insulin pens and automated delivery technologies. Although many automated insulin-delivery advances have focused on type 1 diabetes, selected technologies may support insulin-treated people with T2DM. Continuous glucose monitoring (CGM) can reveal glucose patterns that HbA1c alone cannot show and can support safer titration in people using insulin or medicines associated with hypoglycaemia. Glucose-responsive insulin, sometimes described as smart insulin, is a longer-term research goal. Such systems would increase insulin activity when glucose rises and reduce activity as glucose falls, potentially lowering hypoglycaemia risk. However, clinically reliable glucose-responsive insulin remains investigational. Delivery systems must respond rapidly, predictably and safely across meals, exercise, illness and changing insulin sensitivity. Other research directions include once-weekly basal insulin formulations and improved delivery devices. These innovations should be evaluated for pharmacokinetics, immunogenicity, dosing errors, device usability and real-world affordability, not only pharmacological novelty.

15. β-cell preservation and regeneration

A durable cure for T2DM would require more than temporary glucose lowering; it would need to preserve or restore adequate β-cell function. Research explores reducing β-cell stress, improving cellular survival, stimulating replication, inducing neogenesis from progenitor-like cells and reprogramming other pancreatic cell types. Regeneration biology has identified potential pathways, but translation is difficult because adult human β-cells have limited proliferative capacity and the diabetic pancreas is exposed to chronic metabolic stress (De Leu et al., 2024).VA successful regenerative therapy would need to generate mature, glucose-responsive β-cells in adequate numbers without causing uncontrolled proliferation, tumour formation, hypoglycaemia or abnormal hormone secretion. It would also need to address the underlying insulin resistance and metabolic environment that contributed to β-cell failure. Regeneration may therefore be more effective when combined with weight management, anti-inflammatory strategies or therapies that reduce glucotoxicity and lipotoxicity. At present, β-cell regeneration remains an investigational research field rather than a clinically established treatment for routine T2DM.

16. Cell replacement, transplantation and regenerative medicine

Cell replacement strategies seek to restore insulin-producing capacity by transplanting donor islets, stem-cell-derived islet cells or engineered pancreatic cells. Much of the clinical development has focused on type 1 diabetes, where autoimmune destruction is the dominant cause of insulin deficiency. Translation to T2DM is more complex because insulin resistance, obesity, systemic inflammation and ongoing metabolic stress may compromise transplanted-cell function. Immunosuppression, graft survival, vascularization, cell maturity and manufacturing consistency are major barriers. Encapsulation technologies aim to protect transplanted cells from immune attack while permitting oxygen, nutrients and insulin to pass. Gene editing and engineered cell lines may improve resistance to immune destruction, but safety concerns remain. For T2DM, cell replacement may ultimately be relevant to carefully selected individuals with advanced β-cell failure, but it is unlikely to replace therapies that target obesity and insulin resistance for the majority of patients. Research must establish durable function, acceptable immune risk, scalable production and cost-effectiveness before broad clinical adoption.

17. Precision medicine and diabetes subtyping

T2DM is clinically heterogeneous. People with similar HbA1c values may differ in age at onset, body composition, insulin resistance, β-cell reserve, genetic risk, liver fat, cardiovascular risk and propensity for complications. Cluster analyses have proposed subgroups based on age, BMI, HbA1c, insulin resistance and β-cell function. Such approaches suggest that therapeutic response and complication risk may vary across biologically distinct forms of diabetes. Precision medicine aims to match treatment to these differences rather than relying exclusively on a one-size-fits-all algorithm. Potential tools include clinical phenotyping, genetic risk scores, metabolomics, continuous glucose data, imaging of ectopic fat and biomarkers of β-cell function. However, most proposed subtyping systems are not yet sufficiently validated to direct routine prescribing across diverse populations. Algorithms must be tested prospectively and shown to improve outcomes, not merely classify patients. Generalizability is particularly important because many datasets are drawn from populations that may not represent South Asian, African or other underrepresented groups. Precision medicine should complement, not delay, proven risk-reducing treatment.

18. Gut microbiome-directed interventions

The gut microbiome influences energy harvest, bile-acid metabolism, intestinal permeability, inflammation and production of short-chain fatty acids. Differences in microbial composition have been associated with T2DM, although diet, medication use, geography and disease duration complicate causal interpretation. Proposed interventions include dietary fibre, prebiotics, probiotics, synbiotics, defined microbial consortia and faecal microbiota transplantation (FMT). Early clinical studies suggest that selected interventions may modestly affect insulin sensitivity or glycaemic measures, but findings are heterogeneous. Microbiome-directed therapy is not currently a substitute for evidence-based glucose-lowering medicines. FMT carries risks of transmitting infectious organisms and requires rigorous donor screening and regulatory oversight. Probiotic effects are strain-specific; evidence for one preparation cannot be generalized to all products. A recent review emphasizes that clinical validation remains incomplete and that larger, well-designed trials are needed before microbiome interventions can be recommended as standard T2DM treatment (Haneesh et al., 2026). Research should establish durable effects, identify responders and clarify whether microbial changes cause metabolic improvement or simply accompany it.

19. Metabolic and bariatric surgery

Metabolic surgery can produce substantial and sometimes durable improvements in glycaemia, body weight and cardiometabolic risk among people with obesity and T2DM. Procedures such as Roux-en-Y gastric bypass and sleeve gastrectomy affect food intake, gut hormones, bile-acid signalling, nutrient flow and insulin sensitivity. Diabetes remission is possible, particularly in people with shorter disease duration and preserved β-cell function, but remission is not guaranteed and relapse can occur. Long-term follow-up is necessary to monitor nutritional deficiencies, weight recurrence, gastrointestinal complications and diabetes recurrence. Comparative research continues to examine surgery against modern pharmacotherapy. A 2024 systematic review and meta-analysis assessed long-term outcomes of metabolic surgery compared with pharmacological treatment, reflecting the need to evaluate outcomes beyond the first postoperative year (Yang et al., 2024). Surgery should be considered within multidisciplinary care and according to clinical eligibility, patient preference, operative risk and local guidance. It is not a failure of medical therapy, nor is it appropriate for every patient. Emerging high-efficacy

medicines may change the balance of risks and benefits, making direct comparative trials increasingly important.

20. Liver-directed and metabolic inflammation approaches

Metabolic dysfunction-associated steatotic liver disease (MASLD) and its inflammatory fibrotic form, metabolic dysfunction-associated steatohepatitis (MASH), commonly coexist with T2DM. Liver fat contributes to hepatic insulin resistance and excess glucose production. Weight loss and improved insulin sensitivity can reduce liver fat, while selected GLP-1-based therapies and pioglitazone may have benefits in some people with T2DM and MASH. ADA guidance recognizes the importance of considering liver disease when selecting glucose-lowering therapy (American Diabetes Association Professional Practice Committee, 2025). Other investigational strategies target hepatic lipid synthesis, inflammation, fibrosis and bile-acid pathways. These approaches may be useful for patients whose liver disease progresses despite lifestyle and metabolic treatment. However, improvement in liver enzymes or imaging does not necessarily prove prevention of cirrhosis, liver failure or mortality. Histological endpoints and long-term clinical outcomes are needed. In T2DM, liver-directed treatment is likely to be integrated with weight reduction, cardiovascular risk management and glucose-lowering medicines rather than used in isolation.

21. Safety, tolerability and long-term monitoring

The expanding therapeutic landscape increases the importance of structured safety monitoring. Incretin-based therapies commonly cause gastrointestinal symptoms, which can be reduced through gradual dose escalation and individualized counselling. Clinicians should consider dehydration risk when vomiting or diarrhoea occurs, and evaluate persistent or severe abdominal symptoms. SGLT2 inhibitors require counselling about genital infections, volume depletion and ketoacidosis risk. Finerenone requires potassium and kidney-function monitoring. Insulin and sulfonylureas require attention to hypoglycaemia, particularly when other medicines are added. Long-term safety cannot be inferred from short phase II trials. Rare adverse events, effects in pregnancy, interactions with multiple medicines, outcomes in frail older adults and safety in advanced kidney or liver disease require dedicated evaluation. Weight-loss therapies also raise questions about lean mass, bone health, nutritional adequacy and what happens after discontinuation. Shared decision-making should explain expected benefits, uncertainty, warning symptoms and monitoring requirements. Pharmacovigilance and real-world evidence are essential after approval because trial populations may not fully reflect routine clinical practice.

22. Access, affordability and health-system implementation

Therapeutic innovation has limited public-health value if medicines are inaccessible. High-cost injectable therapies may be difficult to obtain in lower- and middle-income countries, where T2DM prevalence is rising and healthcare resources are constrained. Availability, reimbursement, cold-chain requirements, supply continuity, trained prescribers and patient education all influence real-world effectiveness. In Bangladesh and similar settings, treatment decisions must consider affordability, local registration, medicine quality, continuity of supply and the capacity to monitor adverse effects. Generic medicines, rational prescribing, lifestyle support and reliable access to essential therapies remain crucial. New high-efficacy agents should be evaluated not only by clinical trial efficacy but also by cost-effectiveness and budget impact. Health systems can improve outcomes through team-based care, pharmacist-led medication review, diabetes education, blood-pressure and lipid management, kidney screening and foot and eye services. Digital health and telemedicine may support follow-up, but should not widen inequities for people with limited connectivity or digital literacy.

23. Role of pharmacists and multidisciplinary care

Pharmacists have an important role in translating therapeutic advances into safe and effective care. Their contributions include checking dose titration, identifying contraindications and interactions, supporting adherence, counselling about injection technique and storage, recognizing adverse effects and reinforcing sick-day guidance. When a GLP-1 RA or tirzepatide is added to insulin or a sulfonylurea, pharmacists can help identify the need for prescriber-led dose reassessment to reduce hypoglycaemia. For SGLT2 inhibitors, counselling about genital hygiene, hydration and ketoacidosis warning signs is valuable. A multidisciplinary model involving physicians, pharmacists, nurses, dietitians, diabetes educators and mental-health professionals can address the complexity of T2DM. Therapeutic success depends on more than selecting a molecule: patients need understandable

information, practical follow-up, nutrition support, physical-activity planning and access to complication screening. Pharmacists can also support pharmacovigilance by documenting suspected adverse drug reactions and medication errors. In resource-limited settings, trained pharmacists may help improve rational medicine use and reduce unnecessary duplication or inappropriate combinations.

24. Research gaps and future directions

Several gaps remain before emerging therapies can transform routine T2DM care. First, head-to-head trials are needed to compare new multi-agonists with established high-efficacy agents using clinically relevant endpoints. Second, cardiovascular, kidney and liver outcome trials must determine whether improvements in surrogate markers translate into fewer complications and deaths. Third, research should assess lean-mass preservation, nutritional status, bone health, mental health and treatment durability. Fourth, studies should include older adults, people with advanced CKD, diverse ethnic groups and populations from low- and middle-income countries. For regenerative and microbiome approaches, the priority is to move from mechanistic promise to reproducible human evidence. Precision-medicine algorithms require prospective validation and cost-effectiveness analysis. Pharmaceutical development should also consider oral formulations, less frequent dosing, stable room-temperature products and affordable manufacturing. Finally, discontinuation studies are important because chronic metabolic disease may recur when treatment stops. The next generation of T2DM therapy will be judged by sustained health outcomes, safety, accessibility and patient-centred value not by HbA1c reduction alone.

25. Critical discussion

The most immediate therapeutic advances are those supported by robust randomized trials and clear clinical indications. Tirzepatide demonstrates the potential of dual incretin agonism, while SGLT2 inhibitors and GLP-1 RAs have established roles in cardiorenal risk reduction. Semaglutide's FLOW results and finerenone outcome data reinforce the importance of treating kidney risk as a central component of diabetes care. By contrast, triple agonists, oral small-molecule GLP-1 candidates and newer amylin combinations remain dependent on ongoing development and regulatory assessment. A recurring challenge is the tendency to interpret dramatic weight-loss findings as proof of broad diabetes benefit. Weight loss is important, but long-term clinical value also depends on cardiovascular outcomes, kidney outcomes, adverse events, lean mass, adherence and affordability. Likewise, mechanistic novelty does not guarantee meaningful patient benefit. β-cell regeneration, cell replacement, microbiome manipulation and precision medicine may eventually change the disease model, but they are less mature than incretin and SGLT2 therapies. A balanced review must therefore separate established evidence from plausible future directions and avoid overstating preliminary results.

26. Conclusion

Emerging therapeutic approaches are changing T2DM management from a narrow focus on glucose reduction to a broader strategy addressing weight, cardiovascular risk, kidney disease, liver disease and underlying metabolic dysfunction. Dual GIP/GLP-1 receptor agonism has already expanded treatment options, while triple agonists, oral small-molecule GLP-1 agents and amylin-based combinations represent promising directions. SGLT2 inhibitors, GLP-1 RAs and finerenone illustrate the value of organ protection beyond glycaemic control. Metabolic surgery remains an effective option for appropriately selected patients with obesity and T2DM. At the same time, β-cell regeneration, cell replacement, microbiome-directed therapy and precision medicine remain research frontiers requiring stronger clinical validation. The future is unlikely to depend on one universal medicine. Instead, effective care will combine evidence-based pharmacotherapy, lifestyle intervention, individualized risk assessment, monitoring and equitable access. For pharmaceutical science, the central priorities are durable efficacy, improved tolerability, convenient delivery, rigorous long-term safety and affordability. Clinicians and pharmacists should adopt emerging therapies according to the strength of evidence and local regulatory approval, while avoiding premature use of investigational compounds.

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