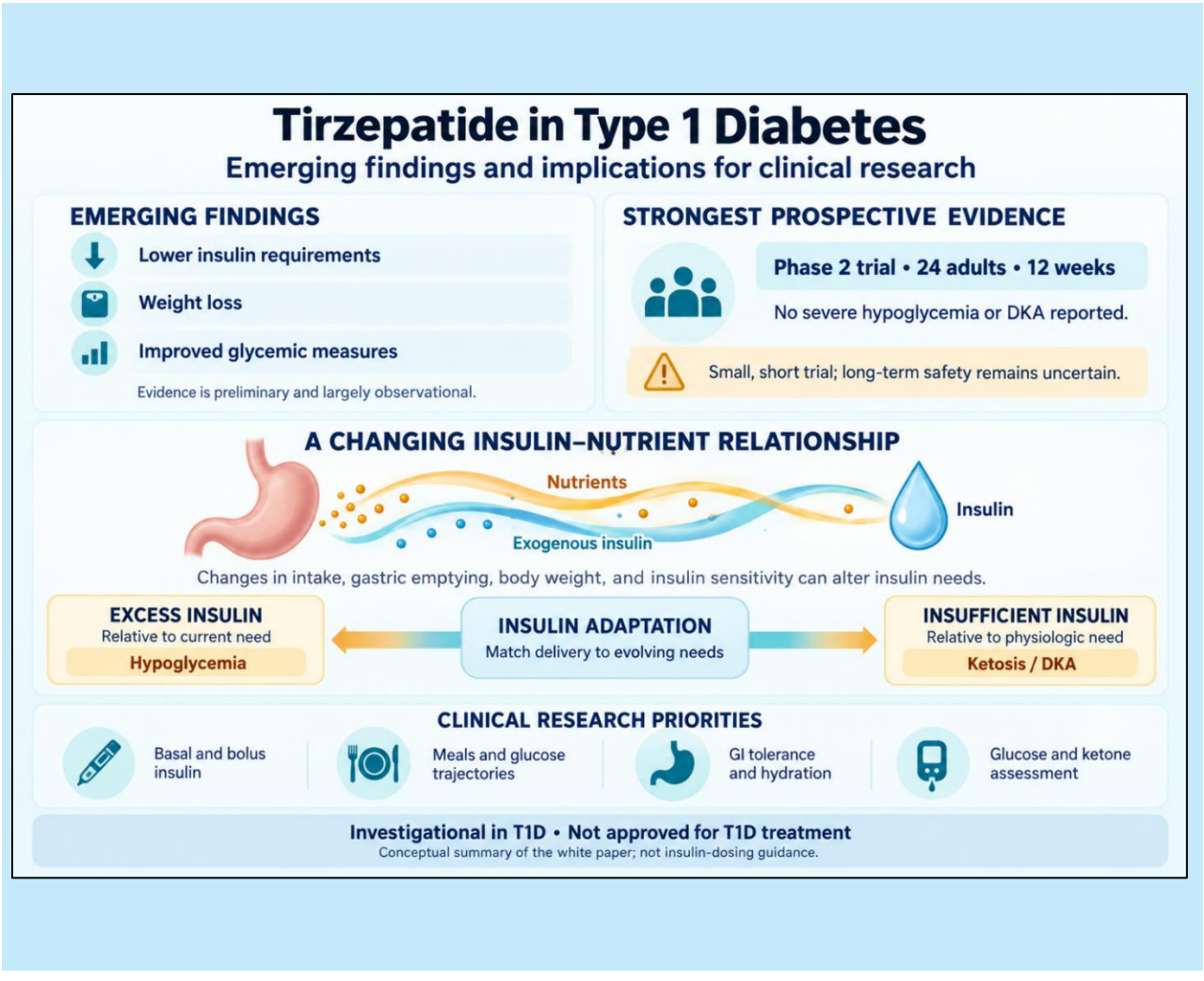
Hypoglycemia Risk With Tirzepatide in Type 1 Diabetes

EMERGING CLINICAL EVIDENCE, MECHANISTIC CONSIDERATIONS, AND IMPLICATIONS FOR CLINICAL RESEARCH

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Hypoglycemia Risk With Tirzepatide in Type 1 Diabetes: Emerging Clinical Evidence, Mechanistic Considerations, and Implications for Clinical Research

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[1] **Evolution Research Group (ERG):** A network of clinical research sites conducting trials across all phases, with specialized expertise in early-phase and complex clinical research in neuroscience, endocrinology, and metabolic disorders. ERG supports clinical conduct, investigator engagement, and scientific leadership across a broad range of therapeutic areas.

[2] **Lotus CRO:** A full-service contract research organization that provides comprehensive clinical trial support, from protocol development through regulatory submission. Lotus works with both ERG-affiliated and independent research sites, with a dedicated focus on metabolism, endocrinology, and other complex therapeutic areas.

ABSTRACT

Tirzepatide, a dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor agonist, is not approved for treatment of type 1 diabetes (T1D). Nevertheless, use of tirzepatide in adults with T1D, particularly those who are overweight or obese, has increased in both clinical practice and investigational settings. The evidence base has evolved from small retrospective cohorts to a randomized phase 2 trial and recent systematic reviews. Across these sources, the most consistent findings are substantial weight loss, improved glycemic metrics, and reduced total daily insulin requirements. Importantly, the emerging tirzepatide-specific literature has not demonstrated a consistent increase in severe hypoglycemia or diabetic ketoacidosis (DKA), although the number of prospectively studied participants remains small and long-term safety is not established.[1–7] The absence of a strong severe-hypoglycemia signal should not be interpreted to mean that hypoglycemia risk is absent. Tirzepatide is administered to individuals with T1D only in the presence of exogenous insulin. Current U.S. labeling warns that concomitant insulin can increase hypoglycemia risk and that insulin dose reduction may be necessary.[8] The central clinical question is therefore not whether tirzepatide is intrinsically hypoglycemic, but how rapidly insulin requirements and nutrient appearance change after treatment and whether insulin delivery adapts appropriately. The broader GLP-1 receptor agonist (GLP-1RA) literature provides historical context. Large liraglutide trials in T1D demonstrated reductions in weight and insulin dose but also identified increased symptomatic hypoglycemia in some dose groups and increased hyperglycemia with ketosis at higher doses.[9,10] More recent meta-analyses have generally not found a statistically significant increase in severe hypoglycemia with GLP-1RA adjunctive therapy, while gastrointestinal adverse effects and ketosis remain important considerations.[11,12] For clinical research, continuous glucose monitoring (CGM) provides dense longitudinal glucose data that can characterize glycemic variability and detect the timing, magnitude, and duration of glucose excursions that may be missed by measurements collected at discrete time points. It should nevertheless be understood as one component of a broader safety and pharmacodynamic strategy. In studies involving early tirzepatide exposure, meal challenges, or gastric-emptying assessments, particular attention should be given to the temporal relationship among prandial insulin action, nutrient appearance, and glucose trajectories.

INTRODUCTION: WHY THE QUESTION IS CHANGING

The therapeutic landscape of T1D has historically been organized around insulin replacement. At the same time, overweight and obesity are increasingly common among adults with T1D, creating interest in adjunctive therapies that can address weight, insulin resistance, and glycemic burden. Tirzepatide, a dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor agonist, has therefore attracted attention despite the absence of a T1D indication.

By 2026, the evidence base includes a small randomized placebo-controlled phase 2 trial, several observational cohorts, analyses of automated insulin delivery (AID), and systematic reviews.[1–7] The scientific question has consequently shifted. Rather than asking only whether tirzepatide can be used in T1D, it is now possible to ask how its metabolic effects alter insulin requirements and what those changes imply for hypoglycemia risk.

This white paper reviews the emerging evidence with a specific focus on hypoglycemia. It also considers the broader GLP-1RA experience in T1D, the pharmacologic importance of gastric emptying and reduced intake, and the relationship between hypoglycemia and the opposing risk of relative insulin deficiency and ketosis.

TIRZEPATIDE-SPECIFIC EVIDENCE IN T1D

Randomized phase 2 evidence

Snaith and colleagues conducted a 12-week, double-blind, placebo-controlled phase 2 trial in 24 adults with T1D and obesity. Tirzepatide was initiated at 2.5 mg once weekly for 4 weeks and increased to 5 mg once weekly for 8 weeks. Tirzepatide produced substantial weight loss and reduced total daily insulin requirements. Despite the reduction in insulin requirements, there were no significant between-group differences in CGM-derived time below range, and no severe hypoglycemia, DKA, or serious adverse events were reported in the tirzepatide group.[1] The study is small and short, but it provides the strongest prospective evidence currently available and did not identify a clear severe-hypoglycemia signal during 12 weeks of treatment.

Observational cohorts

In a single-center observational study of 26 adults with T1D, Akturk and colleagues reported improved HbA1c and CGM-derived time in range during 8 months of tirzepatide treatment. Time below range did not increase. One participant experienced severe hypoglycemia and discontinued treatment; no DKA was reported.[2] The study was retrospective, lacked a control group, and included heterogeneous titration, but it captured real-world insulin-treated T1D.

Garg and colleagues subsequently evaluated 62 adults with T1D and overweight or obesity treated with tirzepatide and reported improvements in HbA1c, body weight, insulin requirements, and CGM metrics over 1 year. No hospitalizations for severe hypoglycemia or DKA were reported.[3] These data extend the observation period but remain subject to confounding, selection bias, and treatment adaptation by experienced clinicians.

A 2026 retrospective propensity score-matched cohort by Purcell and colleagues provides a controlled observational comparison. Twenty-three adults with T1D and overweight or obesity receiving tirzepatide were matched to 23 untreated controls. Over mean follow-up of approximately 28 and 31 weeks, respectively, total daily insulin decreased by 21.82 units/day with tirzepatide compared with an increase of 5.62 units/day among controls. After adjustment for multiple comparisons, time in range, time below range, and coefficient of variation did not differ significantly between groups. Safety ascertainment was limited by the retrospective design, with one episode of symptomatic hypoglycemia and no DKA reported.[4]

Automated insulin delivery and the insulin-requirement signal

A focused analysis of 11 adults from the previously reported observational cohort who were using Tandem Control-IQ is particularly informative for mechanism.[5] Within 2 months of tirzepatide initiation, median total daily insulin declined from 73.9 to 51.7 units/day. Basal insulin declined from

47.0 to 32.4 units/day and bolus insulin from 31.4 to 17.9 units/day. Despite these reductions in insulin, time in range increased by a median 12.9 percentage points, HbA1c declined, and time below range (<70 mg/dL) did not increase.[5]

The relative reduction in bolus insulin was greater than the reduction in basal insulin, and recorded carbohydrate intake also declined.[5] This pattern supports a clinically important interpretation: tirzepatide can rapidly change the amount and distribution of insulin required to maintain glucose control. Hypoglycemia risk therefore depends heavily on whether insulin delivery adapts to the new metabolic state.

Systematic synthesis

A 2026 meta-analysis of six observational studies involving 248 adults found a mean reduction in total daily insulin of approximately 24 units/day at 6 months, accompanied by reductions in HbA1c and body weight. Gastrointestinal symptoms were the most commonly reported adverse effects, and no major safety signal was identified, although adverse-event ascertainment was limited across the observational evidence base.[6] A separate 2026 systematic review that incorporated the randomized phase 2 trial and seven observational studies judged the overall certainty of evidence to be low or very low and emphasized that the absence of a consistent short-term signal for severe hypoglycemia or DKA should not be interpreted as proof of long-term safety.[7]

THE APPARENT PARADOX: LESS INSULIN, NOT LESS CONTROL

The emerging tirzepatide literature shows that insulin requirements can fall substantially, sometimes within the first several weeks of treatment, yet CGM studies have not shown a corresponding increase in time below range and prospective evidence has not identified a clear severe-hypoglycemia signal.[1–7] A recent matched observational cohort strengthens this interpretation by demonstrating a substantial reduction in total daily insulin relative to untreated controls without a significant between-group difference in time below range.[4]

This is not necessarily paradoxical when the exposure-response system is considered dynamically. Exogenous insulin requirement is not fixed. It reflects carbohydrate intake, hepatic glucose production, insulin sensitivity, physical activity, body mass, illness, and other physiologic variables. Tirzepatide can alter several of these determinants simultaneously. If insulin delivery is reduced in parallel with falling requirement, glucose exposure can improve without increasing hypoglycemia. If insulin delivery does not adapt, the same physiologic shift can create excess relative insulin exposure.

A drug may therefore have low intrinsic hypoglycemic potential while still creating a setting in which an unchanged insulin regimen becomes excessive. U.S. prescribing information explicitly recognizes this interaction and advises consideration of insulin dose reduction when tirzepatide is initiated with insulin.[8]

MECHANISMS THAT MAY MODIFY HYPOGLYCEMIA RISK

Glucose-dependent incretin pharmacology

Tirzepatide stimulates insulin secretion in a glucose-dependent manner and lowers glucagon secretion.[8] In people without absolute insulin deficiency, glucose dependence helps limit hypoglycemia when tirzepatide is used without insulin or an insulin secretagogue. In T1D, exogenous insulin remains indispensable. Consequently, the dominant hypoglycemia question is the relationship between administered insulin and changing metabolic requirements.

Reduced energy and carbohydrate intake

Reduced appetite and gastrointestinal adverse effects are among the most consistent pharmacodynamic and tolerability effects of tirzepatide.[6–8] In the Control-IQ cohort, recorded carbohydrate intake declined after tirzepatide initiation while bolus insulin requirements fell even more prominently than basal requirements.[5] A mismatch between falling carbohydrate intake and unchanged prandial insulin would be expected to increase hypoglycemia risk.

Changing insulin sensitivity and body mass

Weight loss and changes in insulin sensitivity can

progressively reduce insulin requirements. This mechanism operates on a different time scale from acute gastrointestinal effects. Early insulin adaptation may therefore need to account for immediate changes in intake, whereas later adaptation may increasingly reflect weight loss and altered insulin sensitivity. The available observational data suggest that a large proportion of the reduction in insulin requirements can occur early after treatment initiation.[5]

Gastric emptying and nutrient-insulin temporal discordance

Tirzepatide delays gastric emptying, and the effect is greatest after initial exposure and diminishes with repeated administration.[8,13] In a phase 1 study using acetaminophen absorption as a surrogate for gastric emptying, a single tirzepatide dose at the higher doses studied reduced acetaminophen peak concentration and delayed time to peak concentration; this effect attenuated with repeated dosing.[13]

This mechanism is particularly relevant in T1D because prandial insulin is administered exogenously and its absorption kinetics are not automatically slowed when gastric emptying is delayed. If insulin action begins before carbohydrate appearance, an early downward glucose excursion can theoretically be followed by later postprandial hyperglycemia. The magnitude of this effect at specific low tirzepatide doses has not been established in T1D, so it should be treated as a mechanistic consideration rather than a proven clinical outcome.

WHAT THE EARLIER GLP-1RA EXPERIENCE ADDS

The ADJUNCT ONE trial randomized 1,398 adults with T1D to liraglutide or placebo in addition to insulin. Liraglutide reduced HbA1c, body weight, and insulin requirements, but symptomatic hypoglycemia increased in the 1.8 mg and 1.2 mg groups, and hyperglycemia with ketosis increased significantly with 1.8 mg.[9] ADJUNCT TWO, involving 835 participants with capped insulin doses, similarly demonstrated metabolic benefit but identified higher symptomatic hypoglycemia with liraglutide 1.2 mg and more hyperglycemia with ketosis at 1.8 mg.[10]

These trials show that adjunctive incretin therapy can improve metabolic outcomes while simultaneously changing the safety profile of insulin treatment. They should not, however, be treated as direct estimates of tirzepatide risk. Tirzepatide has distinct dual-receptor pharmacology, contemporary AID and CGM use is more common, and insulin-management strategies have evolved.

A 2024 meta-analysis of 24 GLP-1 analogue trials involving 3,377 participants found no statistically

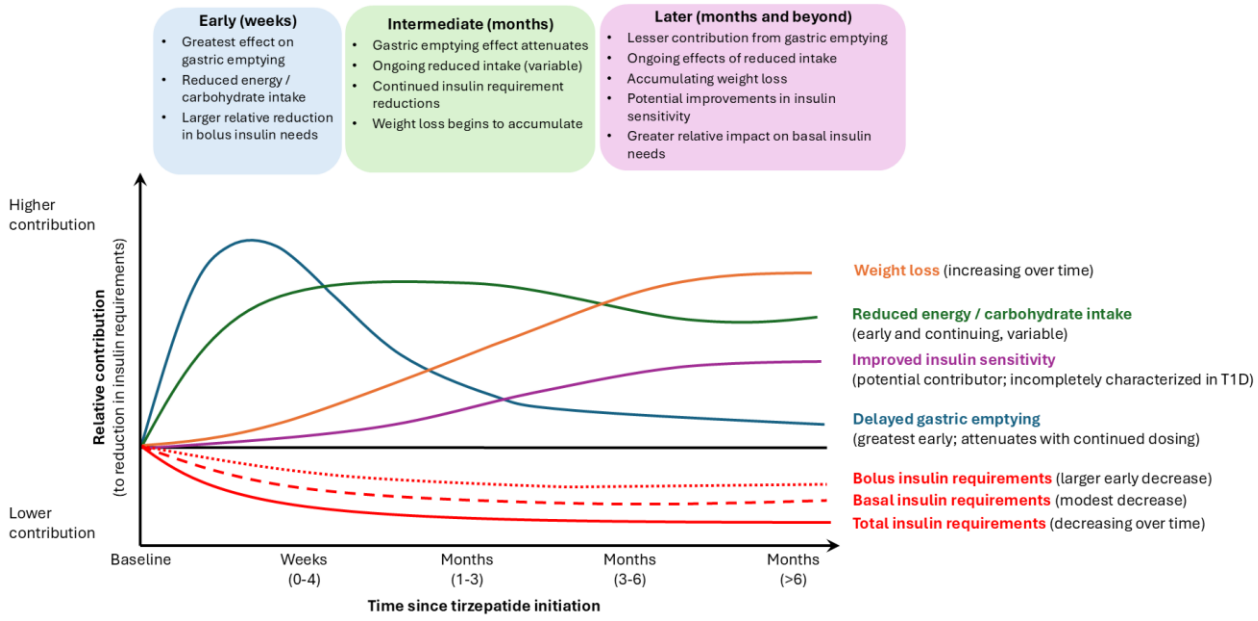


Figure 1. Conception time course of factors that may lower insulin requirements after tirzepatide initiation in T1D. The relative contributions of individual mechanisms are expected to change over time and may overlap. Delayed gastric emptying is greatest after initial tirzepatide exposure and attenuates with repeated dosing, while reduced energy and carbohydrate intake may alter prandial insulin requirements early in treatment. With continued treatment, accumulating weight loss and potential improvements in insulin sensitivity may contribute increasingly to reductions in overall insulin requirements. Available AID data suggest that bolus insulin requirements may decline proportionally more than basal requirements early after initiation.[5,8,13] The figure is a conceptual synthesis and is not intended to define discrete physiologic phases or provide insulin-dosing guidance.

significant increase in severe or symptomatic hypoglycemia, although overall hypoglycemic events and ketosis were increased in pooled analyses, with dose-dependent associations observed for several liraglutide-related adverse effects.[11] A 2026 safety meta-analysis of 25 studies found a neutral pooled risk for overall hypoglycemia and no significant increase in severe hypoglycemia or DKA, while nausea, vomiting, and treatment withdrawal were increased.[12] Thus, severe hypoglycemia is not an inevitable consequence of GLP-1RA adjunctive therapy, but gastrointestinal effects and inadequate adaptation of insulin delivery can create clinically relevant risk.

HYPOGLYCEMIA AND KETOSIS AS OPPOSITE ERRORS OF INSULIN ADAPTATION

Hypoglycemia should not be evaluated in isolation from ketosis. In T1D, the same clinical decision that reduces hypoglycemia risk can increase ketosis risk if insulin is reduced too aggressively. This creates a bidirectional safety problem.

This framework reconciles seemingly competing safety concerns. The objective is not simply to reduce insulin when tirzepatide is initiated. It is to maintain sufficient basal insulin while adapting prandial and total insulin exposure to evolving intake, glucose patterns, and insulin sensitivity.

A published case report illustrates the lower-insulin side of this framework. A woman with T1D using a closed-loop insulin system developed DKA after months of tirzepatide treatment in the setting of marked weight loss, nausea, vomiting, poor intake, and volume depletion. Laboratory glucose was markedly elevated while CGM glucose was discordantly low. The report illustrates how gastrointestinal intolerance, hydration status, sensor performance, and insulin delivery can interact.[14] It does not establish a comparable risk after a single or low-dose exposure, but it cautions against treating CGM as an infallible substitute for direct glucose and ketone assessment.

IMPLICATIONS FOR CLINICAL RESEARCH

The current evidence supports a more specific

Physiologic state	Insulin relationship	Potential consequence
Reduced intake, delayed nutrient appearance, or improved insulin sensitivity	Insulin exposure exceeds current requirement	Hypoglycemia
Appropriate insulin adaptation	Insulin exposure tracks changing requirement	Improved glycemia with lower insulin requirement
Excessive insulin reduction, interruption, or delivery failure	Insulin exposure falls below physiologic requirement	Ketosis and potentially DKA

research question than whether tirzepatide simply increases the risk of hypoglycemia. Clinical studies should characterize how rapidly insulin requirements change, which components of insulin delivery change first, and whether glucose excursions cluster around meals, gastrointestinal symptoms, or dose escalation.

Insulin-management algorithms should distinguish basal from prandial insulin and should avoid reflexive reductions that could compromise basal insulin sufficiency. The Control-IQ data suggest that bolus requirements may fall proportionally more than basal requirements, but these findings come from only 11 participants and should not be generalized into a universal titration rule.[5] As summarized in Figure 1, the relative contributions of factors lowering insulin requirements may change and overlap over time. Early adaptation may be influenced particularly by reduced energy and carbohydrate intake and delayed nutrient appearance, whereas accumulating weight loss and potential improvements in insulin sensitivity may contribute increasingly with continued treatment.

CGM is particularly useful as a pharmacodynamic tool because it can quantify time below range, time in range, glycemic variability, and the temporal relationship of glucose excursions to meals and insulin dosing. In early-phase studies, however, clinically consequential CGM values should be interpreted in conjunction with capillary or venous glucose, particularly when symptoms or hydration status are discordant with sensor readings.[14]

Ketone monitoring deserves parallel attention. Gastrointestinal intolerance, reduced intake, insulin interruption, or unexpected hyperglycemia can create relative insulin deficiency even when glucose is not profoundly elevated. Prespecified blood beta-hydroxybutyrate assessment can therefore complement glucose monitoring in protocols designed to evaluate adjunctive incretin therapy in T1D.

Meal standardization and documentation of prandial insulin timing become especially important when gastric emptying is a pharmacodynamic endpoint or when early post-dose physiology is under study. Without such standardization, it can be difficult to distinguish a drug-related change in nutrient appearance from differences in meal composition, insulin timing, or rescue carbohydrate administration. When within-meal ingestive behavior is itself relevant, objective methods such as the Universal Eating Monitor can additionally characterize the amount and temporal pattern of food consumption.[15] Synchronized assessment of food intake, prandial insulin administration, and CGM trajectories could provide a more integrated characterization of nutrient-insulin temporal relationships.

EVIDENCE GAPS AND RESEARCH PRIORITIES

Several evidence gaps remain. First, the randomized tirzepatide evidence in T1D is based on a small 12-week phase 2 trial, and most longer-duration data are observational.[1–7] Longer observational follow-up has been reported, but it cannot provide the controlled exposure or systematic safety ascertainment needed to establish long-term safety or reliably estimate uncommon outcomes such as severe hypoglycemia and DKA. Larger and longer randomized trials are therefore needed to characterize both the durability of metabolic effects and clinically important safety outcomes with useful precision.

Second, dose-response relationships remain inadequately characterized in T1D. The randomized phase 2 trial evaluated tirzepatide only through 5 mg weekly, while observational cohorts have included broader and heterogeneous dose exposure.[1,3,4] Although real-world studies include participants receiving maintenance doses of 10 to 15 mg, available sample sizes and nonrandomized dose escalation do not permit reliable characterization of dose-dependent effects on insulin requirements, glycemic outcomes, or hypoglycemia risk. Future studies should therefore evaluate whether the magnitude or timing of insulin adaptation and associated safety outcomes differ across clinically relevant tirzepatide doses.

Third, insulin adaptation has not been standardized across studies. Future trials should prospectively capture basal and bolus insulin changes, insulin per kilogram, carbohydrate intake, AID settings, rescue

carbohydrate use, and the timing of changes relative to tirzepatide initiation and escalation.

Fourth, the relationship between tirzepatide-induced gastric-emptying changes and glucose excursions in T1D remains poorly characterized. Simultaneous assessment of gastric emptying, CGM, standardized meal exposure, and insulin timing could determine whether nutrient-insulin temporal discordance is clinically meaningful.

Fifth, existing studies largely involve adults with overweight or obesity. Safety and insulin-response patterns may differ in leaner adults with T1D, individuals with impaired awareness of hypoglycemia, established gastroparesis, recurrent DKA, or substantial residual C-peptide. Adolescents with T1D also remain largely unstudied and represent an important additional evidence gap. Future studies should prospectively assess these populations and characterize relevant baseline features so that safety and insulin-response findings can be interpreted in relation to age and clinical phenotype rather than leaving these sources of heterogeneity undefined.

Sixth, contemporary AID systems may materially change the risk profile of adjunctive incretin therapy. A 2024 expert consensus concluded that GLP-1RAs have potential as adjunctive treatment in adults with T1D using AID, while emphasizing the need for further prospective evidence and careful system adaptation.[16] The interaction among pharmacotherapy, sensor performance, and algorithmic insulin delivery should therefore be treated as a distinct research domain rather than assumed to reproduce older multiple-daily-injection experience.

Seventh, generalizability beyond specialist diabetes care remains uncertain. Much of the available evidence derives from endocrinology settings in which insulin dosing, CGM data, and treatment tolerability can be actively reviewed and therapy adjusted.[3,4] Reassuring safety findings obtained under these conditions may not fully characterize outcomes in settings with less intensive glucose surveillance or insulin-management support. Future studies should therefore evaluate whether insulin-adaptation patterns and safety outcomes remain consistent across different models and intensities of diabetes care.

Finally, the treatment trajectory beyond tirzepatide initiation remains incompletely characterized in T1D. Available evidence suggests that insulin requirements may change rapidly after initiation, but individual pharmacodynamic effects may follow different trajectories with continued exposure and dose escalation.[5] Future studies should characterize whether changes in insulin requirements, nutrient intake, gastric emptying, body weight, and glycemic outcomes attenuate, persist, or evolve as tirzepatide doses increase. The consequences of treatment interruption, discontinuation, and reinitiation also warrant prospective study, including whether insulin requirements and other metabolic effects reverse at the same rate at which they emerge during treatment. These questions are particularly relevant to defining appropriate monitoring and insulin adaptation across the full treatment course rather than only during initiation.

CONCLUSIONS

Current tirzepatide-specific evidence has not demonstrated a consistent increase in severe hypoglycemia in adults with T1D, even though insulin requirements can decline substantially.[1–7] The evidence remains preliminary, and absence of a signal is not equivalent to proof of safety.

The most useful conceptual model is dynamic rather than categorical. Tirzepatide can alter energy intake, gastrointestinal physiology, gastric emptying, body weight, and insulin sensitivity. These changes can lower insulin requirements. Hypoglycemia occurs when insulin exposure exceeds the evolving requirement; ketosis occurs when insulin adaptation overshoots in the opposite direction and produces relative insulin deficiency.

For clinical development, this framework argues for integrated assessment of insulin dose, meal exposure, CGM trajectories, direct glucose measurements when clinically indicated, gastrointestinal tolerance, hydration, and ketones. CGM is valuable, but the broader scientific objective is to understand and

manage the changing relationship between exogenous insulin and nutrient availability.

Tirzepatide in T1D should therefore remain an investigational strategy. The emerging evidence is sufficiently reassuring to support continued study, but sufficiently incomplete to require deliberate risk characterization rather than extrapolation from type 2 diabetes or obesity.

EVIDENCE SUMMARY

Evidence source	Design	Key insulin/glycemic finding	Hypoglycemia / DKA finding	Interpretive value
Snaith et al[1]	Phase 2 RCT; n=24	Lower total daily insulin; improved HbA1c and weight	No severe hypoglycemia or DKA reported	Strongest prospective tirzepatide-specific evidence
Akturk et al[2]	Observational; n=26	TIR improved; insulin dose declined	1 severe hypoglycemia; no DKA	Real-world CGM evidence
Garg et al[3]	Retrospective frequency-matched cohort; 62 treated, 37 controls	Improved HbA1c, weight, insulin, CGM metrics	No hospitalizations for severe hypoglycemia or DKA	Longer real-world follow-up
Purcell et al[4]	Retrospective propensity-matched cohort; 23 treated, 23 controls	TDD decreased 21.82 U/day vs +5.62 U/day in controls; no significant adjusted between-group difference in TIR or TBR	1 symptomatic hypoglycemia episode; no DKA reported; safety ascertainment limited	Controlled observational support for reduced insulin requirement without increased TBR
Karakus et al[5]	AID analysis; n=11	~ 30% TDD reduction by 2 mo; bolus fell more than basal	Time <70 mg/dL did not increase	Mechanistic insulin-adaptation signal
Soliman et al[6]	Meta-analysis; 6 observational studies, n=248	TDD fell ~24 U/day at 6 mo	No major safety signal identified; safety ascertainment limited	Quantifies insulin reduction; observational limitations
Acucella & Caponio[7]	Systematic review; 1 RCT + 7 observational studies	Weight and insulin signals consistent	Long-term safety remains uncertain	Emphasizes low certainty
ADJUNCT ONE / TWO[9, 10]	Large liraglutide RCTs	Lower weight and insulin requirements	Some increased symptomatic hypoglycemia and ketosis	Historical GLP-1RA precedent
GLP-1RA meta-analyses[11, 12]	24-25 studies	Modest glycemic/weight/insulin benefit	No clear pooled increase in severe hypoglycemia; overall hypoglycemia, ketosis, and GI events increased in some analyses.	Broader class context

Abbreviations: RCT, randomized clinical trial; DKA, diabetic ketoacidosis; TIR, Time in Range; CGM, continuous glucose monitoring; TDD, Targeted drug delivery; TBR, time below range ; AID, automated insulin delivery; mo, months; GLP-1RA, Glucagon-like peptide-1 receptor agonists; GI, gastrointestinal.

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