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Evaluating Tirzepatide with Lifestyle Modification in Overweight Adults with Type 2 Diabetes: A Real-World Clinical Study

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Abstract: ***This real-world clinical study assessed the effectiveness of tirzepatide, a dual GIP/GLP-1 receptor agonist, in combination with structured lifestyle modification among adults with type 2 diabetes and overweight or obesity. Conducted through a virtually assisted diabetes care platform, the 8-week intervention enrolled 41 participants who received tirzepatide starting at 2.5 mg, with some escalating to 5 mg based on response. Of the participants, 31 continued treatment and completed an 8-week follow-up, exhibiting significant weight reduction (4.56 ± 2.97; p <0.001). Subgroup analysis revealed significantly greater weight loss in the 5 mg dose-escalation group compared to the 2.5 mg group (5.22 ± 3.63 kg vs. 3.84 ± 1.94 kg; p<0.001). Significant reductions were also observed in BMI, waist circumference, and blood glucose levels, with dose-dependent trends evident. Adverse events were predominantly mild and transient, primarily gastrointestinal in nature. The combined pharmacologic and lifestyle approach demonstrated promising efficacy and safety in short-term diabetes management, highlighting tirzepatide's potential role in real-world integrated care models.***

Keywords: Tirzepatide, Type 2 Diabetes, Lifestyle Intervention, Overweight, Glycemic Control

1. Introduction

Obesity and type 2 diabetes (T2D) prevalence has escalated globally, affecting over one billion individuals and contributing significantly to morbidity and healthcare burden [1]. Obesity, particularly excess visceral adipose tissue, drives insulin resistance, adipose tissue dysfunction, lipid metabolic disturbances, and progressive β-cell failure, ultimately increasing the risk of cardio-renal complications and other associated morbidities. Effective weight reduction has been consistently shown to attenuate these complications, slow T2D progression, and improve metabolic outcomes, highlighting the significance of integrated weight- and glucose-lowering strategies in disease management [2].

Central to implementing these strategies is the accurate assessment of adiposity and glycemic control, which is critical for diagnosis, risk stratification, and monitoring therapeutic response [3]. Notably, for Asian populations, the ADA recommends adjusted BMI cutoffs due to their higher risk of T2D at lower BMI levels compared to other populations. Specifically, BMIs of 23.0-27.4 kg/m² and ≥27.5 kg/m² are categorized as overweight and obese, respectively [4]. Glycated hemoglobin A1c (HbA1c) reflects average glycemia over 2-3 months, with thresholds for normal (<5.7%), prediabetes (5.7-6.4%), and diabetes (≥6.5%). Fasting blood glucose (FBS) offers a snapshot of basal glycemia, with normal values <100 mg/dL, impaired fasting glucose 100-125 mg/dL, and diabetes ≥126 mg/dL. Collectively, these metrics not only guide clinical decision-making but also provide objective endpoints for evaluating the efficacy of emerging therapeutic interventions [4, 5].

Therapeutic strategies for obesity and T2D have evolved over decades to address complex pathophysiological defects while balancing efficacy and safety [6]. Lifestyle modification (diet and exercise) remains foundational due to its safety and broad metabolic benefits; however, its effects on glycemic control and weight reduction are frequently modest, often limited by lack of personalized guidance, ongoing motivation, and structured adherence support, which contribute to poor long-term compliance [7]. To overcome these challenges, more intensive therapies have been developed. As summarized in Table 1, the evolution of therapeutic approaches reflects increased metabolic potency and mechanistic targeting. The introduction of bariatric surgery in the 1950s marked a pivotal advance, achieving dramatic weight loss and, in numerous cases, diabetes remission. Nonetheless, bariatric surgery is invasive, carrying significant perioperative risks and potential for long-term nutrient deficiencies, underscoring the ongoing need for safe, effective non-surgical alternatives that optimize metabolic outcomes and support sustained adherence [8, 9].

Table 1: Evolution of therapeutic approaches

Therapeutic approaches	Therapeutic Evolution period
Lifestyle Modification (Diet + Exercise)	Pre-1950s-present
Bariatric Surgery	1950s-present
SGLT2 Inhibitors	~2010s-present
GLP-1 RAs	Mid 2000s-present
Dual GIP/GLP-1 RA (Tirzepatide)	2022-present

Pharmacologic therapies expanded options by targeting specific pathophysiological defects in T2D [10]. Dipeptidyl peptidase-4 (DPP-4) inhibitors (e.g., sitagliptin, vildagliptin)

prolong endogenous incretin activity to enhance glucose-dependent insulin secretion. Being weight neutral, their utility is limited in obese individuals with T2D [11, 12]. Sodium-glucose cotransporter-2 (SGLT2) inhibitors (e.g., empagliflozin, dapagliflozin) reduce hyperglycemia by inhibiting renal tubular glucose reabsorption, thereby increasing urinary glucose excretion and inducing osmotic diuresis with associated caloric loss. These actions confer modest reductions in HbA1c and body weight, but their clinical utility is limited by an elevated incidence of urinary tract and genital mycotic infections, as well as adverse events related to volume depletion (e.g., dehydration, dizziness, and hypotension) [13, 14]. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs; liraglutide, semaglutide) provide significant improvements in glycemic control and weight reduction, though their single-pathway mechanism limits full metabolic impact. They mainly enhance insulin secretion and slow gastric emptying but do not address peripheral insulin resistance, GIP-mediated adipose metabolism, or α-cell dysfunction [15, 16].

Dual GIP/GLP-1 receptor agonists such as tirzepatide overcome these mechanistic limitations through integrated incretin receptor activation to target multiple T2D defects. This dual action enhances β-cell function, improves insulin sensitivity, modulates adipose tissue metabolism, and promotes satiety. Compared with single-receptor agents, tirzepatide achieves superior glycemic control and weight reduction by simultaneously amplifying glucose-dependent insulin secretion, suppressing inappropriate glucagon release, optimizing postprandial glucose regulation, and reducing caloric intake. Through integrated pancreatic and extrapancreatic effects, tirzepatide offers a unique therapeutic profile tackling hyperglycemia and adiposity beyond what prior therapies achieved [17, 18].

Through integrated pancreatic and extrapancreatic effects, tirzepatide offers a unique therapeutic profile tackling hyperglycemia and adiposity beyond what prior therapies achieved. This novel mechanism constitutes the pharmacodynamic rationale for its clinical efficacy and safety profile, which was recognized by the U.S. Food and Drug Administration's approval in 2022, a landmark event in the non-surgical management of obesity and T2D. This approval reflects tirzepatide's demonstrated ability to improve blood sugar control and reduce weight, which is attributed to its glucose-dependent insulinotropic action, alongside a favorable safety profile characterized by transient, dose-dependent gastrointestinal side effects and a low risk of hypoglycemia when used as monotherapy or with non-insulin agents [19]. Importantly, when combined with structured lifestyle modification (LSM), tirzepatide maximizes metabolic benefits, improves adherence, and mitigates challenges seen with prior pharmacologic and surgical interventions, offering a comprehensive, dual-targeted, minimally invasive approach to obesity and T2D care.

Within this evolving therapeutic landscape, the present study investigates the real-world effectiveness of tirzepatide in combination with LSM over 8 weeks, under physician supervision and personalized, structured health coaching. Primary outcomes include glycemic control, weight reduction, metabolic improvements, and treatment tolerability, contextualized by historical pharmacologic and surgical outcomes. By leveraging a dual incretin, non-insulin, and non-invasive strategy, this study addresses prior therapy limitations, generating pragmatic evidence supporting tirzepatide combined with LSM as a potent adjunctive treatment for integrated obesity and T2D management.

2. Epidemiology

Epidemiological Link Between Overweight and T2D

The contemporary epidemiological profile of T2D is tightly correlated with the global escalation in overweight and obesity prevalence, with central adiposity recognized as the primary population-level determinant of incident T2D across diverse geographic populations. Longitudinal surveillance data have consistently documented persistent, age-standardized increases in the prevalence of both conditions over recent decades, indicative of widespread secular trends rather than isolated regional phenomena [20, 21]. Globally, over 1.9 billion adults are classified as overweight, with 650 million meeting criteria for obesity; notably, approximately 88% of adults diagnosed with T2D present with concurrent overweight or obesity. A robust dose-response relationship has been demonstrated wherein increasing body mass index (BMI), waist circumference, and waist-to-hip ratio are each associated with incrementally higher T2D risk and earlier hyperglycemia onset. Furthermore, the temporal precedence of adiposity relative to dysglycemia, coupled with data from randomized clinical trials and real-world longitudinal cohorts revealing risk attenuation via intentional weight loss, substantiates a causal association extending beyond simple correlation [22].

This global epidemiological convergence has been driven by profound shifts in dietary and lifestyle factors, including expanded availability and consumption of ultra-processed foods, elevated dietary glycemic load, pervasive sedentarism, and reduced non-exercise activity thermogenesis. These lifestyle determinants operate synergistically with demographic shifts such as population aging to enlarge the pool at risk for dysglycemia and subsequent T2D. Consequently, substantial upward trends in both incidence density and disease prevalence have been observed worldwide, especially pronounced in regions undergoing rapid socioeconomic transformation [23]. In the United States, where 34% of adults meet criteria for obesity, over 11% of adults aged 20 years or older have been diagnosed with diabetes, highlighting the frequent coexistence of adiposity with T2D [24]. Similarly, epidemiological data from Africa demonstrate a high prevalence of overweight and obesity among T2D cases, with reports indicating 81.3% from Nigeria, and ranges of 40.1-44.9% and 24.5-39.9% from Northern Tanzania and Sudan, respectively [25-27]. Australia exhibits a comparable pattern, with 32.8% of patients with T2D classified as overweight and 53% as obese. Collectively, these findings emphasize the substantial population-attributable fraction of excess adiposity for incident T2D, suggesting that effective mitigation of overweight and obesity could avert a significant proportion of new diabetes cases across epidemiological contexts [28].

Table 2: Global and Regional Prevalence of Overweight and Obesity in Non-Diabetic Adults and Among Adults with T2D.

Region / Country	Prevalence of Overweight/Obesity in Non-Diabetic Adults	Prevalence of Overweight/Obesity Among Adults with T2D	BMI Thresholds
Global [23]	1.9 billion overweight; 650 million obese	~88% of adults with T2D	BMI ≥25 kg/m² overweight; ≥30 kg/m² obese (WHO)
United States [24]	34% obese	>11% of adults ≥20 years have diabetes; high co-prevalence	BMI ≥25 kg/m² overweight; ≥30 kg/m² obese
Nigeria (Africa) [25]	-	81.3% overweight/obese at T2D diagnosis	BMI ≥25 kg/m² overweight; ≥30 kg/m² obese
Northern Tanzania (Africa) [26]	-	44.9% overweight; 40.1% obese	BMI ≥25 kg/m² overweight; ≥30 kg/m² obese
Sudan (Africa) [27]	-	39.9% overweight; 24.5% obese	BMI ≥25 kg/m² overweight; ≥30 kg/m² obese
Australia [28]	-	32.8% overweight; 53% obese	BMI ≥25 kg/m² overweight; ≥30 kg/m² obese
East Asia - Korea [29]	-	37.8% (1998) → 54.4% (2020) obese	BMI ≥23 kg/m² overweight; ≥27.5 kg/m² obese (Asian cut-off)
East Asia - Japan [30]	-	32.1% (2000) → 40.9% (2012) obese	BMI ≥23 kg/m² overweight; ≥27.5 kg/m² obese
East Asia - China [31]	4.2% (1993) → 15.7% (2015) obese	-	BMI ≥23 kg/m² overweight; ≥27.5 kg/m² obese
South Asia - India [32]	NFHS-4: M 20.7%, F 19.6% → NFHS-5: M 23.7%, F 24%	>88% abdominal obesity among T2D patients	BMI ≥23 kg/m² overweight; ≥27.5 kg/m² obese.

In non-diabetic cohorts, the rising prevalence of overweight and obesity has consistently preceded and predicted subsequent increases in T2D incidence, with central adiposity measures offering particularly robust risk stratification [33, 34]. Longitudinal cohort studies demonstrate that even modest weight gain during adulthood substantially elevates T2D risk, whereas intentional weight loss imparts measurable protective effects, underscoring the principle of reversibility at the population level. These relationships are particularly pronounced within Asian subpopulations, including South Asians, where metabolic risk manifests at lower body mass index (BMI) thresholds due to disproportionate visceral adiposity and ectopic fat accumulation, a phenotype commonly referred to as the "South Asian phenotype." This distinct metabolic profile has prompted major clinical guidelines to endorse lower BMI thresholds for overweight and obesity classifications in Asian populations [5, 35]. Epidemiological data from India further illustrate this association: the National Family Health Survey-5 (NFHS-5) reports that 23.7% of men and 24% of women are overweight, with over 88% of adults diagnosed with T2D also exhibiting abdominal obesity. Within these cohorts, anthropometric indices of abdominal adiposity, including waist circumference and waist-to-height ratio, provide enhanced risk discrimination, consistent with early-onset insulin resistance and dysglycemia observed even in individuals with BMI values traditionally classified as normal [36].

The multifactorial and interconnected drivers of this epidemiological transition include shifts in food systems characterized by increased consumption of energy-dense, nutrient-deficient foods and sugar-sweetened beverages, alongside irregular meal frequency and elevated dietary glycemic load, all contributing to exacerbated postprandial hyperglycemia. Environmental factors such as urban planning that discourages active transportation, increased sedentary occupations, and pervasive screen time exacerbate the risk profile. Moreover, circadian disruptions secondary to short sleep duration, shift work, and psychosocial stressors have been epidemiologically linked to increased adiposity and incident diabetes. Life-course exposures, ranging from low birthweight and childhood stunting followed by rapid catch-up growth to intergenerational effects conceptualized within the developmental origins of health and disease framework, further augment metabolic susceptibility. Additional modifying factors encompass socioeconomic disparities, rural-to-urban migration, healthcare access inequalities, pharmacologic influences (e.g., weight-promoting psychotropics), and exposure to potential endocrine-disrupting chemicals [37, 38]. Health system contributions, including evolving diagnostic criteria, intensified screening protocols, and improved survival among individuals with diabetes, have also advanced case detection, capturing both genuine rises in incidence and earlier identification of prediabetes and early T2D [39].

When synthesizing evidence from prospective cohorts, natural experiments, Mendelian randomization studies, and intervention trials spanning lifestyle, pharmacologic, and surgical modalities, the link between overweight and T2D robustly satisfies Bradford Hill criteria for causality. These include strength and consistency of association, temporality, biological gradient, biological plausibility, coherence, and experimental confirmation. This convergent evidence solidifies the interpretation of excess adiposity as a primary etiologic driver of the global diabetes epidemic, elucidating the parallel increase in overweight prevalence and diabetes incidence worldwide [40].

This epidemiological nexus carries significant implications for disease surveillance and public health policy. Given the heterogeneity in metabolic risk profiles across populations, monitoring paradigms should expand beyond BMI to include central adiposity indices such as waist circumference and waist-to-height ratio, applying population-specific thresholds, including lower cutoffs for Asian populations. Public health strategies must address upstream determinants of adiposity and dysglycemia, prioritize interventions targeting high-risk demographics such as urban youth, women with histories of gestational diabetes, and individuals with rapid weight gain, and integrate approaches that concurrently manage weight and glycemic control. These comprehensive and precision-targeted interventions are essential to attenuate the intersecting epidemics of overweight

and T2D, thereby fostering sustainable, population-level prevention [41, 42].

3. Pathophysiology

The pathophysiology of T2D is characterized by a multifaceted interplay between peripheral insulin resistance and progressive dysfunction of pancreatic β-cells, culminating in chronic hyperglycemia and widespread metabolic disturbances. Excess visceral adiposity exacerbates this pathological environment through adipocyte enlargement, aberrant adipokine secretion, and persistent low-grade inflammation, collectively compromising insulin signaling and disrupting glucose homeostasis. Understanding these molecular mechanisms elucidates the pathobiological connections between obesity and T2D and provides the scientific basis for therapeutic interventions such as dual GIP/GLP-1 receptor agonists like tirzepatide, which aim to restore metabolic and endocrine balance.

Molecular Pathways Underlying Overweight/Obesity-Associated T2D

Chronic caloric surplus initiates a cascade of metabolic alterations, beginning with hypertrophy and hyperplasia of white adipose tissue (WAT), predominantly within visceral depots. The resulting hypertrophic adipocytes undergo endoplasmic reticulum (ER) stress, mitochondrial dysfunction, and hypoxia-induced signaling mediated by hypoxia-inducible factor-1α (HIF-1α) [43]. This cellular stress response triggers the secretion of elevated pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and monocyte chemoattractant protein-1 (MCP-1), which propagate both local and systemic low-grade inflammation [44].

The inflammatory milieu activates downstream signaling pathways including c-Jun N-terminal kinase (JNK) and nuclear factor kappa B (NF-κB), resulting in serine phosphorylation of insulin receptor substrate proteins (IRS-1/2). This modification impairs phosphatidylinositol 3-kinase (PI3K)-Akt signaling, which is critical for GLUT4 translocation in skeletal muscle and adipose tissue. Consequently, glucose uptake is reduced, leading to hyperglycemia and compensatory hyperinsulinemia that places further stress on pancreatic β-cells [45, 46].

Concurrently, hypertrophic WAT contributes to central metabolic dysregulation through leptin resistance. This resistance, mediated by overactivation of suppressor of cytokine signaling 3 (SOCS3) and protein tyrosine phosphatase 1B (PTP1B) within hypothalamic neurons, results in blunted anorexigenic pro-opiomelanocortin (POMC) signaling [47]. Simultaneously, decreased adiponectin secretion attenuates AMP-activated protein kinase (AMPK) activation in liver and skeletal muscle, reducing fatty acid oxidation and fostering ectopic lipid deposition. This accumulation of excess lipids and their toxic metabolites within tissues creates a harmful environment, termed lipotoxicity, which exacerbates peripheral insulin resistance [48].

Consequently, these metabolic disturbances also extend to the incretin system, where in T2D complicated by obesity, glucose-dependent insulinotropic polypeptide (GIP) receptor signaling in pancreatic β-cells becomes attenuated, alongside insufficient secretion of glucagon-like peptide-1 (GLP-1). These alterations impair glucose-dependent insulinotropic effects. Persistent hyperglucagonemia caused by α-cell dysregulation further exacerbates hepatic glucose production and contributes to sustained postprandial hyperglycemia and aberrant nutrient processing [49].

Moreover, central resistance to leptin and insulin enhances orexigenic neuropeptide Y (NPY)/agouti-related peptide (AgRP) neuronal activity, while suppressing anorexigenic POMC signaling, thereby driving hyperphagia. The resultant impairment in satiety signaling perpetuates positive energy balance, further driving visceral fat accumulation and metabolic dysfunction. [50].

This expanded visceral adiposity releases elevated levels of circulating free fatty acids (FFAs), which activate Toll-like receptor 4 (TLR4)-mediated NF-κB signaling pathways in hepatocytes and myocytes, thereby promoting pro-inflammatory gene expression and exacerbating insulin resistance. In parallel, this inflammatory cascade, together with persistent hyperglucagonemia and impaired insulin-mediated Akt phosphorylation, triggers upregulation of key hepatic gluconeogenic enzymes such as phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase) via transcription factors FOXO1 and CREB, thereby enhancing hepatic gluconeogenesis. The resulting persistent fasting and postprandial hyperglycemia further intensifies systemic insulin resistance [43, 51].

Collectively, the convergence of adipose tissue inflammation, adipokine imbalance, impaired incretin signaling, central appetite dysregulation, ectopic lipid accumulation, and enhanced hepatic gluconeogenesis establishes a self-amplifying pathophysiological loop. This integrated dysregulated signaling network connects overweight and obesity directly to hyperglycemia, β-cell overload, progressive insulin resistance, and the accelerated onset and progression of T2D [52].

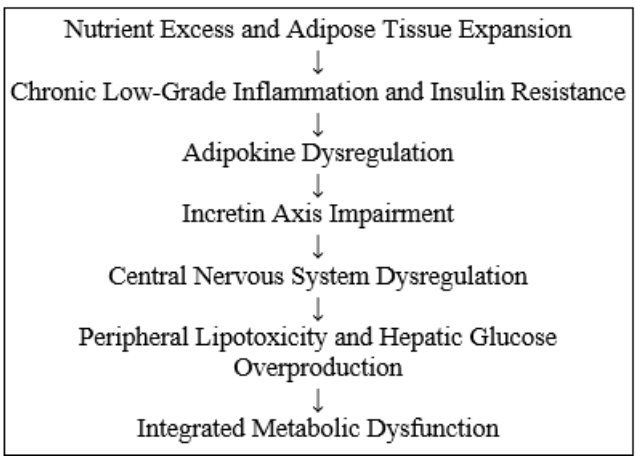

Figure 1: Molecular Pathophysiology of Overweight and Obesity in T2D

Mechanism of Action of Tirzepatide: Dual GIP and GLP-1 Receptor Agonism

Tirzepatide is a next-generation synthetic peptide uniquely engineered to function as a dual agonist for the GIP receptor and GLP-1 receptor, both belonging to the class B G-protein-coupled receptor (GPCR) family. This dual receptor targeting enables a coordinated modulation of peripheral and central metabolic pathways, crucial for restoring glucose homeostasis and achieving energy balance [53].

Initially, Tirzepatide binds with high affinity and specificity to GIP receptors, primarily expressed on pancreatic β-cells and adipocytes [54]. Concurrently, it engages GLP-1 receptors found on pancreatic β-cells and α-cells, as well as in the gastrointestinal tract and hypothalamic neurons involved in appetite regulation. The complementary receptor activation produces multiple beneficial effects on metabolism by stimulating key hormonal pathways, including increasing insulin release, reducing glucagon levels, slowing stomach emptying, and controlling appetite [55].

Upon GIP receptor activation on pancreatic β-cells, tirzepatide stimulates adenylate cyclase via heterotrimeric Gs protein coupling, leading to increased intracellular cyclic adenosine monophosphate (cAMP), an essential secondary messenger. This elevated cAMP activates downstream effectors including protein kinase A (PKA) and cAMP2 (Epac2), which synergistically promote glucose-dependent insulin granule exocytosis. This restores β-cell insulin secretion responsiveness, often impaired in T2D due to GIP resistance, thereby enhancing endogenous insulin release aligned with ambient glucose levels [54, 56].

Simultaneously, GLP-1 receptor engagement on β-cells amplifies glucose-dependent insulin secretion through a parallel cAMP-mediated pathway. Beyond β-cells, activation of GLP-1 receptor on pancreatic α-cells inhibits dysregulated glucagon secretion, which is a pathophysiological hallmark in T2D contributing to excessive hepatic glucose production. This suppression of glucagon curtails hepatic gluconeogenesis, thereby mitigating fasting hyperglycemia and improving overall glycemic control [57]. Moreover, GLP-1 receptor agonism extends to the gastrointestinal tract, where it modulates gastric motility by delaying gastric emptying. This action is mediated via the vagal and enteric neuronal pathways, attenuating postprandial glucose excursions and promoting satiety to reduce caloric intake [58].

Complementing these peripheral gastrointestinal effects, tirzepatide's central nervous system activity plays a pivotal role in appetite suppression and weight reduction. Specifically, tirzepatide modulates hypothalamic appetite-regulating neurons by activating anorexigenic pro-opiomelanocortin (POMC) neurons while concurrently inhibiting orexigenic neuropeptide Y (NPY) and agouti-related peptide (AgRP) neurons. This targeted neuronal modulation leads to decreased appetite and food intake, facilitating a negative energy balance conducive to weight loss [59].

Beyond central nervous system actions, tirzepatide also exerts important peripheral effects on adipose tissue metabolism. Activation of GIP receptors in adipocytes enhances lipoprotein lipase (LPL) activity, promoting hydrolysis of circulating triglycerides and subsequent lipid uptake. Simultaneously, tirzepatide stimulates insulin-dependent translocation of glucose transporter type 4 (GLUT4) to the adipocyte membrane, resulting in improved glucose uptake and utilization. Together, these processes enhance adipose tissue insulin sensitivity, optimize energy partitioning, preserve lean muscle mass, and reduce visceral adiposity, key factors driving metabolic health restoration [54, 59, 60].

The integrated pharmacodynamic synergy arising from dual GIP and GLP-1 receptor activation underlies tirzepatide's superior incretin effect compared to single receptor agonists. This manifests clinically as enhanced pancreatic β-cell function, sustained glucose homeostasis, reduced glucotoxic stress on β-cells, diminished hepatic glucose output, and robust appetite suppression. Collectively, these effects translate into significant reductions in fasting and postprandial glucose levels, marked weight loss, and improved insulin sensitivity [61].

In essence, the stepwise, multi-organ mechanism of action of tirzepatide highlights its therapeutic superiority by concurrently targeting the diverse pathophysiological pathways responsible for T2D and obesity. This dual receptor agonism paradigm positions tirzepatide as a transformative agent in metabolic disease management, offering integrated control over glycemic and weight parameters.

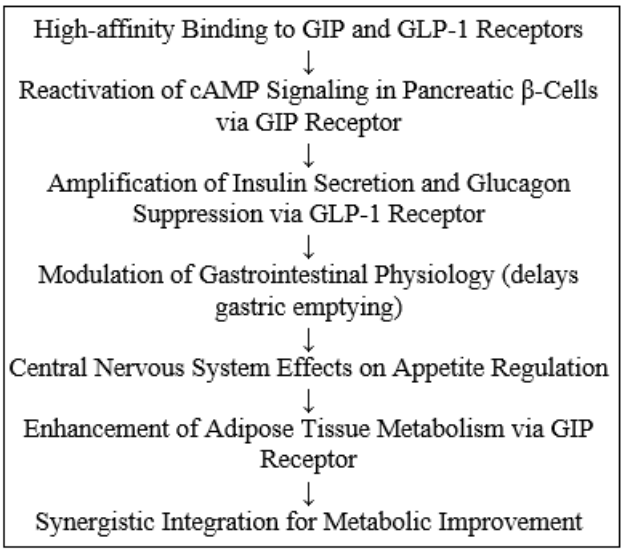

Figure 2: Stepwise, detailed mechanistic pathway underscores tirzepatide's therapeutic superiority

4. Methodology

This study evaluated the 8-week outcomes of tirzepatide therapy in 41 T2D subjects with an initial BMI of 25 or greater (obesity) with diabetes. Tirzepatide therapy was initiated at 2.5 mg and titrated sequentially to 5 mg, for a few participants, with dose escalation guided by clinical response, tolerability, and achievement of glycemic targets, under continuous medical supervision. Clinical outcomes were

assessed from initiation to discontinuation over the treatment period.

Study Design

This retrospective, real world study was conducted as part of Sugarfit's Diabetes Reversal and Management Program, a virtual, physician- and coach-assisted diabetes care. Dosage levels varied across participants, reflecting real-world treatment patterns.

Study participants

The study population comprised adults aged ≥18 years with T2D and concurrent overweight or obesity, enrolled according to predefined eligibility criteria. All participants initiated tirzepatide therapy at 2.5 mg administered subcutaneously once weekly during the initial 4-week run-in period. Subsequent dose escalation to 5 mg was undertaken only if clinically required, guided by individual glycemic response, weight reduction, and tolerability, thereby mimicking real-world prescribing practice. Participants were evaluated at week 4, and week 8 with stratification at each time point based on the actual tirzepatide dose received. Clinical assessments included anthropometric parameters, and glycemic indices along with symptomatic side-effect monitoring. Retention was tracked, and discontinuations were recorded in cases of adverse events, complication loss to follow-up, or achievement of targeted metabolic goals as mentioned in the discontinuation criteria below. A flow diagram (Figure 3) illustrates participant enrollment, longitudinal retention, dose distribution, and discontinuation across study follow-up.

Enrolled: N = 41
↓
Weeks 1-4 (2.5 mg): $n_4 = 41$ **(**All participants initiated on 2.5 mg; Therapy cessation (n = 10) due to loss to follow-up, or attainment of metabolic goals/voluntary withdrawal)
↓
Weeks 5-8: $n_8 = 31$ **(**Continued on 2.5 mg (n = 15); Escalated to 5 mg (n = 16); All 31 completed 8 weeks of follow-up).

Figure 3: Participant enrollment, dose escalation, retention, and therapy cessation over 8 weeks of tirzepatide therapy in Individuals with T2D and overweight/obesity.

Inclusion criteria:

- Adults aged ≥18 years with a confirmed diagnosis of T2D (HbA1c ≥6.5%).
- Overweight or obesity, defined as BMI ≥23 kg/m² or ≥25 kg/m².

Exclusion criteria:

Participants were excluded from prescribing tirzepetide if they met any of the following conditions:

- Diagnosis of type 1 diabetes, latent autoimmune diabetes in adults (LADA), or maturity-onset diabetes of the young (MODY).
- Pregnant or breastfeeding women.
- History of medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia type 2 (MEN 2).
- Presence of severe gastrointestinal conditions such as gastroparesis or pancreatitis.
- Severe renal or hepatic impairment.
- History of diabetic retinopathy.
- Known hypersensitivity to tirzepatide or any of its excipients.
- Prior bariatric surgery due to increased risk of pancreatitis.
- Age below 18 years or above 70 years.

Therapeutic Strategy: Tirzepatide and Lifestyle Intervention

Following a 2-week screening period, eligible participants received tirzepatide injection as an adjunct to a structured LSM program for 8 weeks. The LSM program encompassed individualized dietary counseling and supervised physical activity under the oversight of health coaches and physicians, ensuring alignment with standard clinical care for T2D management and weight loss.

Tirzepatide Administration and Dose Escalation:

All study participants were initiated on tirzepatide 2.5 mg administered subcutaneously once weekly during the 4-week dose-initiation phase. This introductory regimen was implemented to assess drug tolerability and mitigate the incidence of gastrointestinal adverse events (GI AEs), which represent the most frequent dose-limiting toxicities associated with incretin-based therapies.

Subsequent dose escalation followed a structured, protocol-driven stepwise approach, with incremental increases of 2.5 mg for the next 4 weeks. Escalation was contingent upon clinical response and tolerability, ensuring individualized optimization. Participants who tolerated tirzepatide well were advanced to the next dosing tier, regardless of early weight or glycemic response. Conversely, individuals achieving glycemic or weight targets, or experiencing dose-limiting gastrointestinal intolerance, hypoglycemia, or other adverse reactions, were stabilized at their existing dose.

Tirzepatide injections were delivered into standard subcutaneous anatomical sites (abdomen, thigh, or upper arm), with mandatory site rotation to minimize the risk of lipohypertrophy, localized induration, or injection-site hypersensitivity reactions. Participants were trained in aseptic injection technique and adherence protocols. In the event of a missed dose, administration within 96 hours (4 days) of the scheduled injection was permitted; beyond this interval, the regimen was resumed at the next scheduled dosing point, maintaining the weekly pharmacokinetic rhythm.

The escalation scheme was supported by the pharmacokinetic (PK) and pharmacodynamic (PD) properties of tirzepatide. The molecule exhibits linear, dose-proportional PK with a terminal elimination half-life of ~5 days, ensuring sustained plasma concentrations compatible with once-weekly administration. Its PD actions encompass glucose-dependent insulinotropic activity, suppression of inappropriate glucagon secretion, delayed gastric emptying, and central appetite modulation, all of which necessitate gradual titration to

optimize efficacy while minimizing adverse effects. This dose-escalation framework was consistent with regulatory guidance and clinical practice recommendations, enabling balanced optimization of therapeutic efficacy, safety, and tolerability within the study cohort.

Concomitant Therapy Considerations and Safety Monitoring

As recommended in the literature and regulatory guidance (Gettman, 2023; EMA, 2025; Farzam et al., 2024) [62, 63, 64], concomitant use of DPP-4 inhibitors with tirzepatide was systematically avoided to prevent redundant incretin axis potentiation. Both agents enhance glucose-dependent insulin secretion; co-administration provides no incremental glycemic benefit and may exacerbate gastrointestinal adverse events due to overlapping pharmacodynamic effects.

Tirzepatide demonstrates linear, dose-proportional pharmacokinetics with a terminal half-life of approximately 5 days, supporting once-weekly subcutaneous administration. This predictable PK profile underpins stepwise dose escalation, which is titrated based on individual pharmacodynamic response, including glycemic control, body weight reduction, and tolerability. Tirzepatide's PD effects include augmentation of glucose-dependent insulin secretion, suppression of inappropriate glucagon release, and modulation of gastric motility, which collectively inform individualized titration and monitoring strategies.

Oral hypoglycemic agents, including sulfonylureas, and exogenous insulin were adjusted individually to mitigate hypoglycemia risk, as the combined insulinotropic effects could precipitate symptomatic or severe hypoglycemia (Cleveland Clinic, 2025; Mayo Clinic, 2025) [65, 66]. Capillary blood glucose was monitored frequently, and protocol-driven dose adjustments were implemented.

Continuous assessment of adverse side effects was performed for each participant throughout the study, encompassing gastrointestinal adverse events (nausea, vomiting, diarrhea), attributable to GLP-1 receptor-mediated modulation of gastric motility and central emetogenic pathways. Participants were instructed to maintain adequate oral hydration to prevent pre-renal azotemia and acute kidney injury secondary to volume depletion. Given reports linking GLP-1 receptor agonists to a modestly increased risk of acute pancreatitis, heightened vigilance was applied in individuals with prior bariatric surgery or established pancreatic risk factors, with expedited diagnostic evaluation if clinically indicated [65, 66].

Adjunctive Lifestyle Modification for Tirzepatide

Nutritional Optimization to Support Tirzepatide Efficacy: To support the efficacy of tirzepatide, patients received individualized nutritional counseling aimed at optimizing dietary intake and maintaining metabolic homeostasis. Energy prescriptions were carefully tailored based on patient-specific variables including age, sex, baseline body weight, and physical activity level, with avoidance of very low-calorie diets (<800 kcal/day) to minimize risks such as dehydration, electrolyte imbalance, and gallstone formation. Caloric targets were adjusted upon attainment of target weight to sustain metabolic balance over time.

Complementing these caloric recommendations, protein intake was emphasized at 0.8-1.2 g/kg/day to preserve lean body mass and prevent catabolic processes. Early treatment phases included supplementation with protein-enriched products (e.g., whey isolate, meal replacements) providing 15-20 g protein per serving. Patients were counseled to prioritize protein consumption at meal initiation. Dietary fats comprised 25-30% of total caloric intake, with a focus on polyunsaturated (n-3 and n-6) and monounsaturated fatty acids to enhance micronutrient absorption and mitigate gastrointestinal side effects, while minimizing saturated and trans fats. Carbohydrates accounted for 45-55% of total calories, with daily fiber intake targeted between 20 and 30 grams to support gastrointestinal health and reduce intolerance symptoms common with tirzepatide therapy. Fiber was introduced gradually and intake goals were dynamically modified in response to gastrointestinal symptom severity to optimize tolerance.

Supporting these nutritional strategies, comprehensive nutritional assessments, including dietary recall, anthropometric measurements, and relevant biochemical assays (e.g., serum vitamins D, B12, and iron panels), were conducted prior to treatment initiation to detect and correct micronutrient deficiencies. Hydration was emphasized with daily fluid intake goals of 2 to 3 liters, tailored according to physical activity and environmental context. Given that GLP-1 receptor agonists may blunt thirst perception, patient education reinforced regular hydration using water and low-calorie beverages to maintain volume status and prevent dehydration-related complications while limiting caffeinated drinks.

Ongoing dietary adherence was systematically monitored and integrated with behavioral and physical activity support to ensure safe, sustainable weight management throughout therapy. Dietary restrictions encompassed minimizing foods high in saturated and trans fats, refined carbohydrates, added sugars, excess sodium, alcohol, and dietary irritants such as greasy, overly sweet, or spicy foods to optimize weight loss efficacy and reduce gastrointestinal adverse effects. For patients experiencing significant appetite suppression or gastrointestinal intolerance, tailored counseling encouraged consumption of small, nutrient-dense meals and maintenance of hydration, with consideration of dose modifications when nutritional intake proved insufficient.

Structured Physical Activity for Optimized Pharmacologic Response to Tirzepatide:

Complementary to dietary management, a structured exercise intervention was prescribed to optimize weight reduction, preserve lean muscle mass, and enhance cardiometabolic health outcomes in patients receiving tirzepatide. Patients participated in a combined exercise regimen comprising moderate-intensity aerobic training (e.g., walking, cycling, swimming) performed 150-300 minutes weekly, alongside resistance training targeting all major muscle groups 2-3 times per week.

To maximize adherence and therapeutic efficacy, participation in strength and conditioning (S&C) live sessions were implemented from the initiation of intervention. This integrated approach attenuates the risk of sarcopenia often associated with pharmacologically induced weight loss, improves cardiorespiratory fitness (VO2 max), and potentiates improvements in insulin sensitivity. Progressive exercise load adjustments and compliance monitoring were systematically incorporated within pharmacotherapy follow-up visits to ensure sustained benefit and safety. This structured fitness protocol synergistically complements the pharmacodynamic effects of tirzepatide, thereby translating into superior metabolic and functional outcomes.

Mental Wellness and Behavioral Support During Tirzepatide Therapy

Due to its effect on gastric emptying, tirzepatide often led to gastrointestinal discomfort and altered satiety signaling in study participants. In response to these physiologic and psychological challenges, a comprehensive behavioral support program was implemented. This multidisciplinary intervention incorporated mindfulness-based modalities, such as Yoga Nidra and meditation, each of which have demonstrated utility in reducing stress, enhancing emotional regulation, and increasing patient resilience during treatment. To further optimize patient outcomes and adherence, participants engaged in structured behavioral interventions, including systematic mood and dietary intake journaling. These measures enabled proactive identification of emotional and nutritional triggers linked to fatigue, mood fluctuations, or diminished motivation, factors that can negatively affect persistence with therapy. Emphasis was placed on optimal hydration, recognizing that adequate fluid intake is essential to prevent dehydration and to attenuate cognitive symptoms, including brain fog and low energy. Reinforcement of fitness protocol adherence was integrated with mental health support strategies, providing benefits such as stress reduction, mood stabilization, and improved metabolic function.

Continuous monitoring of sleep hygiene was also prioritized, reflecting its importance in sustaining emotional well-being and promoting long-term treatment compliance. Patients displaying symptoms consistent with depression, anxiety, or social withdrawal were referred for specialist assessment and offered evidence-based interventions, such as counseling or cognitive-behavioral therapy. Collectively, this multi-component, wraparound strategy addressed the interconnected metabolic, gastrointestinal, and psychological domains, thereby supporting maximal therapeutic efficacy and durable patient benefit during tirzepatide therapy.

Statistical analysis

Data were analyzed using descriptive statistics. Changes in primary and secondary efficacy endpoints (body weight, BMI, waist circumference, FBS, and PPBS) from baseline to follow-up were assessed using paired t-tests or Wilcoxon signed-rank tests as appropriate for data distribution. Subgroup analyses comparing fixed-dose (2.5 mg) and dose-escalation (5 mg) groups were performed using independent sample t-tests or Mann-Whitney U tests. Medication score changes and insulin dose adjustments were evaluated using repeated measures ANOVA or equivalent non-parametric tests. A p-value of <0.05 was considered statistically significant. All analyses were conducted using standard statistical software.

Clinical End Points and Assessments

The primary and secondary endpoints of this study were established to evaluate the clinical efficacy of tirzepatide when administered in conjunction with structured lifestyle modification. The primary endpoints included efficacy assessments focused on changes in BMI, weight, FBS, and PPBS, measured from baseline through week 8. Secondary endpoints encompassed efficacy assessments focused on changes in waist circumference, medication score and safety assessments, involving comprehensive symptomatic side effect monitoring throughout the study. Adverse event surveillance included documentation of gastrointestinal symptoms (nausea, vomiting, constipation, gastrointestinal discomfort), neurological effects (lethargy, headache), and any other clinically relevant events. All dose adjustments were protocol-driven, ensuring participant safety and robust assessment of tirzepatide's efficacy, tolerability, and safety profile in adults with T2D and overweight or obesity.

5. Results

Over the 8-week study period, participants enrolled in the SugarFit program demonstrated progressive improvements in anthropometric parameters, including body weight, BMI, and waist circumference alongside favorable changes in glycemic control, as evidenced by reductions in fasting blood glucose (FBS), and postprandial glucose (PPBS). Therapy adherence and dose titration contributed to optimized clinical outcomes, while adverse events, predominantly gastrointestinal (nausea, vomiting, constipation, GI discomfort) and neurological (lethargy, headache), were generally well-tolerated through personalized dietary interventions and protocol-driven dose adjustments. Treatment discontinuations occurred primarily due to adverse events or achievement of predefined metabolic targets. Collectively, these findings underscore the clinical effectiveness of the integrated trizepatide-lifestyle intervention strategy in achieving sustained glycemic control and weight management in adults with T2D and overweight or obesity.

Participant Demographics

The demographic and baseline clinical characteristics of the enrolled cohort (N = 41) are summarized in Table 3. The study population consisted of 31 males and 10 females, with a mean age of 44.59 ± 10.59 years. The average height was measured at 168.99 ± 9.98 cm. At baseline, the mean body weight was 101.06 ± 19.99 kg, and the mean waist circumference was 111.78 ± 15.90 cm, indicating a population with significant adiposity.

Table 3: Demographic characteristics of the study participants

Demographic variable	Value
Number of Participants	41
Gender (M/F)	31/10
Age (Years)	44 ± 10.49
Height (cm)	168.99 ± 10.13

Of the 41 participants enrolled and initiated on tirzepatide 2.5 mg, 10 discontinued during the first 4 weeks due to financial constraints (n=4), non-responders (n=2), discontinuation after achieving goals (n=1), and temporary discontinuation of tirzepatide therapy (n=3). The remaining 31 participants renewed their SugarFit program package and continued through the full 8-week study. Within this cohort, 15 participants remained on a stable 2.5 mg regimen, while 16 underwent dose escalation to 5 mg after week 4

Clinical Efficacy Observations During 4 and 8 weeks

Tirzepatide administration over a 4-week period yielded consistent and clinically meaningful improvements across the overall cohort (N=41), encompassing fundamental anthropometric and glycemic parameters. Specifically, mean BMI decreased significantly from 36.09 ± 7.70 kg/m² to 34.46 ± 7.57 kg/m², reflecting an absolute reduction of 1.63 ± 1.18 kg/m² ($p<0.001$). This weight-related effect was paralleled by a concomitant decline in body weight of 2.9 ± 2.07 kg (from 101.29 ± 21.02 kg to 96.73 ± 20.85 kg, $p<0.001$). Waist circumference, a validated surrogate marker of visceral adiposity and cardiometabolic risk, exhibited a reduction of 2.67 ± 6.35 cm ($p<0.05$). Improvement in glycemic indices occurred in concert, with fasting blood sugar (FBS) concentrations decreasing from 135.29 ± 23.20 mg/dL to 109.51 ± 18.52 mg/dL ($p<0.05$), while postprandial blood sugar (PPBS) declined by 61.3 ± 29.86 mg/dL ($p<0.001$).

Table 4: Changes in Anthropometric and Glycemic Parameters from Baseline to 4 and 8 Weeks of Tirzepatide Therapy in T2D Patients (n=41 at 4 weeks; n=31 at 8 weeks)

4 Weeks (n= 41)				8 Weeks (n= 31)		
Parameters	**Initial**	**Final**	**P-value**	**Initial**	**Final**	**P-value**
BMI	35.18 ± 7.24	34.13 ± 7.39	p<0.001	36.09 ± 7.70	34.46 ± 7.57	p < 0.001
Weight	99.67 ± 19.66	96.68 ± 19.98	p<0.001	101.29 ± 21.02	96.73 ± 20.85	p < 0.001
Waist	109.83 ± 13.85	107.54 ± 13.52	p<0.001	110.86 ± 14.22	108.19 ± 12.92	p < 0.05
FBS	135.4 ± 25.87	111.11 ± 23.89	p<0.001	135.29 ± 23.20	109.51 ± 18.52	p < 0.05
PPBS	183.43 ± 57.38	129.67 ± 24.39	p<0.001	178.4 ± 43.13	117.1 ± 25.86	p < 0.001

Overall, 76% of participants renewed their program and continued treatment beyond the initial cycle, reflecting favorable tolerability and perceived efficacy. As outlined in the participant details, subgroup analyses were subsequently performed to compare outcomes between those who remained on a stable dose and those who underwent dose escalation.

Overall Efficacy Over 8 Weeks of Tirzepatide Therapy

In this cohort of 31 individuals with T2D and overweight/obesity, tirzepatide therapy yielded significant and clinically meaningful improvements reflective of its targeted action on metabolic dysfunction. The mean baseline BMI decreased from 36.09 kg/m² to 34.46 kg/m², indicating a substantial reduction in adiposity. This change facilitates improved metabolic homeostasis through enhanced insulin sensitivity and hormonal regulation, which contributes to a corresponding decline in body weight from 101.29 kg to 96.73 kg, consistent with tirzepatide's dual agonism of GIP and GLP-1 receptors, which centrally suppress appetite and increase energy expenditure to counteract the positive energy balance contributing to obesity.

Waist circumference, a surrogate marker for visceral fat, was reduced from 111.86 cm to 107.1 cm, reflecting a decrease in metabolically deleterious fat depots. This reduction is particularly important given visceral adiposity's role in exacerbating hepatic insulin resistance and impairing pancreatic β-cell function, both of which are central to type 2 diabetes progression. Concomitantly, significant improvements in glycemic parameters were observed, with fasting blood glucose levels dropping from 135.29 mg/dL to 109.51 mg/dL. These outcomes suggest enhanced basal insulin secretion and effective glucagon suppression facilitated by tirzepatide's incretin receptor activation.

Lastly, postprandial blood glucose levels showed a marked decrease, from 178.4 mg/dL to 117.1 mg/dL, signalling improved post-meal glucose control. This effect relates to tirzepatide's capacity to delay gastric emptying and amplify insulinotropic responses, optimizing nutrient absorption and glucose metabolism after food intake. Collectively, these results underscore tirzepatide's multifaceted therapeutic action, simultaneously improving appetite regulation, islet hormone dynamics, and peripheral glucose handling. Such integrated metabolic restoration achieved within an 8-week treatment window denotes tirzepatide as a potent agent for managing the complex pathophysiology of type 2 diabetes and obesity.

Subgroup Analysis by Dosage Pattern

This subgroup analysis evaluated BMI, body weight, waist circumference, FBS, and PPBS as these markers are directly influenced by tirzepatide, respond within short durations, and provide clinically relevant insights into early metabolic changes.

Fixed 2.5 mg Dose (n=15): At week 4, participants maintained on a stable 2.5 mg dose exhibited early metabolic improvements, consistent with tirzepatide's dual GIP/GLP-1 receptor agonism enhancing insulin secretion and modestly promoting weight loss through appetite suppression and improved insulin sensitivity. Mean BMI decreased slightly from 34.52 ± 6.26 to 33.81 ± 6.40 kg/m², a reduction of 0.71 ± 0.51 kg/m². This substantial change was paralleled by an average weight loss of 2.16 ± 1.57 kg, with body weight declining from 102.78 ± 20.55 to 100.62 ± 20.61 kg. Waist circumference decreased by 1.6 ± 2.52 cm, reflecting reductions in central adiposity. Glycemic improvement was evident with fasting blood glucose (FBS) falling by 22.24 ± 22.61 mg/dL from 127.82 ± 17.56 mg/dL to 105.58 ± 16.68, while PPBS level also showed a reduction of 44.45 ± 38.76 mg/dL, decreasing from 175.6 ± 40.11 mg/dL to 131.15 ± 20.81 mg/dL.

By week 8, treatment continuity yielded further reductions. BMI declined from 34.52 ± 6.26 kg/m² to 33.32 ± 6.54 kg/m², increasing cumulative decrease to 1.2 ± 0.66 kg/m². Body

weight continued to reduce from 102.78 ± 20.55 kg to 98.93 ± 20.98, with a total mean loss of 3.84 ± 1.94 kg. Waist circumference remained decreased by 1.66 ± 8.36 cm. Glycemic effects persisted, with FBS reduction totalling 24.42 ± 17.24 mg/dL (dropped from 131 ± 17.56 mg/dL to 106.58 ± 19.16) and PPBS decreasing by 45.37 ± 35.60 mg/dL (reduced from 169.62 ± 40.11 mg/dL to 124.25 ± 24.65 mg/dL). These improvements are consistent with tirzepatide's capacity to enhance pancreatic β-cell insulin secretion, suppress inappropriate glucagon release, and improve systemic glucose utilization while facilitating modest weight loss through appetite regulation.

Table 5: Changes in clinical and glycemic parameters from baseline through weeks 1-8 in participants maintained on the same dosage (2.5 mg).

Week 4 (n= 15) 2.5 mg					Week 8 (n= 15) 2.5 mg				
	Initial	**Final**	**Change**	**p-value**		**Initial**	**Final**	**Change**	**p-value**
BMI	34.52 ± 6.26	33.81 ± 6.40	0.71 ± 0.51	p<0.001	BMI	34.52 ± 6.26	33.32 ± 6.54	1.2 ± 0.66	p<0.001
Weight	102.78 ± 20.55	100.62 ± 20.61	2.16 ± 1.57	p<0.001	Weight	102.78 ± 20.55	98.93 ± 20.98	3.84 ± 1.94	p<0.001
Waist	108.21 ± 12.69	106.51 ± 11.90	1.6 ± 2.52	p<0.5	Waist	108.21 ± 12.69	106.55 ± 12.06	1.66 ± 8.36	p<0.5
FBS	127.82 ± 17.56	105.58 ± 16.68	22.24 ± 22.61	p<0.01	FBS	131 ± 17.56	106.58 ± 19.16	24.42 ± 17.24	p<0.001
PPBS	175.6 ± 40.11	131.15 ± 20.81	44.45 ± 38.76	p<0.01	PPBS	169.62 ± 40.11	124.25 ± 24.65	45.37 ± 35.60	p<0.05

Dose Escalation to 5 mg (n=16): Participants undergoing dose escalation demonstrated progressive metabolic gains attributable to enhanced incretin receptor stimulation and increased peptide exposure over the higher 5 mg dose period. At week 4 (on 2.5 mg), participants demonstrated a reduction in BMI of 0.96 ± 0.73 kg/m² (from 37.57 ± 8.79 to 36.61 ± 8.79 kg/m²), with body weight decreasing by 2.56 ± 1.84 kg (from 99.9 ± 22.03 to 97.34 ± 21.86 kg). Waist circumference declined by 2.17 ± 3.03 cm, reflecting early central adiposity reduction, while FBS fell by 18.57 ± 38.62 mg/dL and PPBS decreased by 44.37 ± 27.31 mg/dL.

Table 6: Changes in clinical and glycemic parameters from baseline through weeks 1-8 in participants undergoing dose escalation from 2.5 mg (weeks 1-4) to 5 mg (weeks 5-8).

Week 4 (n= 16) 2.5 mg					Week 8 (n= 16) 5 mg				
	Initial	**Final**	**Change**	**p-value**		**Initial**	**Final**	**Change**	**p-value**
BMI	37.57 ± 8.79	36.61 ± 8.79	0.96 ± 0.73	p<0.001	BMI	37.57 ± 8.79	35.61 ± 8.47	1.96 ± 1.46	p<0.001
Weight	99.9 ± 22.03	97.34 ± 21.86	2.56 ± 1.84	p<0.001	Weight	99.9 ± 22.03	94.68 ± 21.21	5.22 ± 3.63	p<0.001
Waist	113.35 ± 15.52	111.18 ± 15.08	2.17 ± 3.03	p<0.05	Waist	113.35 ± 15.52	109.73 ± 12.92	3.62 ± 6.35	p<0.05
FBS	136.33 ± 27.40	117.76 ± 30.15	18.57 ± 38.62	p<0.05	FBS	138.73 ± 27.40	111.86 ± 18.31	26.87 ± 19.56	p<0.001
PPBS	166.6 ± 24.58	122.23 ± 19.77	44.37 ± 27.31	p<0.001	PPBS	168.57 ± 24.60	114.28 ± 23.82	54.29 ± 26.07	p<0.001

Following titration to 5 mg for weeks 5 to 8, more pronounced effects were observed. BMI further declined to 35.61 ± 8.47 kg/m², totaling a reduction of 1.96 ± 1.46 kg/m² from baseline (p<0.001). Body weight showed a greater cumulative loss of 5.22 ± 3.63 kg (p<0.001), consistent with enhanced GLP-1-mediated anorexigenic effects and GIP's role in adipocyte lipolysis. Waist circumference further decreased by 3.62 ± 6.35 cm (p<0.05), indicating meaningful reduction in visceral fat. Glycemic parameters paralleled these anthropometric improvements, with FBS reduced by 26.87 ± 19.56 mg/dL (p<0.001) and PPBS decreasing significantly by 54.29 ± 26.07 mg/dL (p<0.001). These effects reflect the synergistic action of GLP-1-mediated appetite and gastric emptying modulation combined with GIP-driven adipocyte and islet signaling, improving both fasting and postprandial metabolic regulation.

Overall, both subgroups demonstrated clinically meaningful improvements in anthropometric and glycemic parameters over 8 weeks. However, the magnitude of response was more pronounced among participants who underwent titration to 5 mg. The progressive reductions in BMI, body weight, waist circumference, FBS, and PPBS across the two dosage patterns illustrate a clear dose–response relationship, wherein greater metabolic and glycemic benefits were achieved with escalation to the higher dose. Importantly, these pharmacologic effects were complemented by structured lifestyle modification support, including personalized guidance from SugarFit health coaches and general physicians, which likely reinforced adherence, optimized behavioral changes, and enhanced the overall therapeutic outcomes. Together, these findings underscore the dose-dependent efficacy of tirzepatide while highlighting the value of integrated expert-led lifestyle support in maximizing clinical benefits.

Safety Profile

The 8-week safety evaluation of tirzepatide demonstrated a tolerability profile consistent with its dual GIP and GLP-1 receptor agonism, characterized primarily by transient gastrointestinal (GI) and systemic adverse effects occurring early in treatment and diminishing with continued therapy and tailored clinical support.

In the fixed-dose cohort (2.5 mg; n=15), adverse events were predominantly mild to moderate. Initial GI disturbances, such as transient loose stools lasting approximately three days post-first dose, were reported but did not significantly impair adherence. Nausea and appetite suppression were common on day one but rapidly declined, with most participants tolerating therapy well by week two. Although some patients retained a degree of symptomatic burden during the early weeks, these effects progressively lessened over time as improved adherence to tailored dietary strategies supported better tolerance. The marked reduction in GI side effects from high incidence at week one to minimal reports by week eight likely reflects both gastrointestinal adaptation and optimized patient education. Additional systemic symptoms, including headache and lethargy, were infrequent and self-limiting.

Notably, no serious adverse events, treatment discontinuations, or any episodes of hypoglycemia were observed, reflecting the safety of dose escalation under close clinical monitoring and protocol-driven reduction of OHA and insulin dosages by physicians.

Conversely, the dose-escalation cohort (2.5 mg to 5 mg; n=16) experienced a higher frequency of transient GI side effects such as diarrhea, vomiting, abdominal cramps, and bloating, particularly in the initial days of escalation. However, unlike the fixed-dose group, side effect severity declined progressively from week 4 through week 8, attributable to gastrointestinal and metabolic adaptation with sustained protocol-driven lifestyle interventions. Transient systemic effects such as administration-day tiredness and mild headaches were also reported but tended to resolve as treatment continued. Adherence to expert-guided lifestyle modification (dietary structure, hydration, and behavior coaching) appeared to accelerate tolerance and reduce symptom intensity. Importantly, no serious adverse events or treatment discontinuations occurred, and no episodes of hypoglycemia were reported, reflecting the safety of dose escalation under physician-directed adjustment of concomitant OHA and insulin regimens.

Comparative analysis suggests that, while a fixed 2.5 mg dose limited escalation-related side effects, persistent symptoms were observed in some patients. In contrast, escalation to 5 mg initially increased GI events but was associated with a more consistent decline in symptom burden and greater metabolic efficacy by week 8. This dose-dependent pattern underscores that gradual upward titration not only enhances clinical outcomes but also promotes tolerability when paired with personalized, structured lifestyle interventions and patient education guided by SugarFit health coaches and physicians. This highlights an important dose-dependent effect, whereby incrementally higher tirzepatide dosing was linked to both superior therapeutic outcomes and a gradual reduction in side effects over time.

Medication Score

The impact of tirzepatide therapy on overall antidiabetic medication requirements was systematically assessed to evaluate pharmacologic de-intensification in conjunction with structured LSM. This dual framework provided an opportunity to examine not only the drug-induced improvements in glycemic control but also how lifestyle measures, emphasizing diet optimization, adequate hydration, and structured physical activity, acted synergistically to reduce therapeutic burden.

In this study, medication scores were systematically recorded to evaluate pharmacologic treatment burden in participants receiving tirzepatide alongside baseline antidiabetic therapies. Monitoring these changes allowed objective quantification of treatment simplification as a marker of the combined effect of incretin pharmacology and lifestyle interventions. At baseline, the overall oral hypoglycemic agent (OHA) medication score for the cohort (n=41 before dropout) was 1.66 ± 1.32. By week 4, this value had declined to 1.09 ± 1.10, indicating a clinically meaningful reduction in the pharmacologic burden of oral agents (**Table 7A**). This downward trend reflects both the incretin-mediated efficacy of tirzepatide and the concurrent implementation of LSM measures. Participants were consistently counseled on structured dietary/fitness interventions, which together complemented pharmacotherapy in reducing reliance on OHA agents.

Table 7A: Change in OHA's Score (n=41; before dropout)

Time points	Medscore
Baseline	1.66 ± 1.32
After 4 Weeks	1.09 ± 1.1

Among this cohort, five participants were maintained on insulin therapy at baseline. As shown in **Table 7B**, progressive dose reductions were achieved across study visits. For example, one participant demonstrated stepwise tapering of insulin degludec from 40 units to 25 units over 8 weeks, accompanied by reductions in insulin aspart from 90 units to 30 units. Another transitioned from glargine 25 units at baseline to 15 units by week 8. Importantly, one individual was able to discontinue insulin therapy altogether after the fourth week of treatment. These adjustments represent tangible insulin-sparing effects, exhibited through tirzepatide's dual pharmacology, enhancing glucose-dependent insulin secretion, suppressing glucagon release, and improving insulin sensitivity, augmented further by the parallel adoption of lifestyle measures that targeted weight reduction and glycemic stability.

Table 7B: Change in insulin regimens over time (n=41)

	Baseline		Week 4		Week 8	
Patient	**Name**	**Units**	**Name**	**Units**	**Name**	**Units**
1	Insulin Degludec	0-0-40	Insulin Degludec	0-0-30	Insulin Degludec	0-0-25
	Insulin Aspart	30-30-30	Insulin Aspart	25-25-25	Insulin Aspart	10-10-10
2	Insulin Degludec+insulin Aspart	34-0-28	Insulin Degludec+insulin Aspart	32-0-24	Insulin Degludec+insulin Aspart	32-0-24
3	Insulin Glargine	0-0-25	Insulin Glargine	0-0-25	Insulin Glargine	0-0-15
4	Insulin Glargine	0-0-12	Stopped	-	-	-
5	Insulin Glargine	0-0-30	Insulin Glargine	0-0-30	Insulin Glargine	0-0-5
	Lispro Insulin 100 IU	18-18-22	Lispro Insulin 100 IU	18-18-22	Lispro Insulin 100 IU	6-0-6

Subgroup analysis of 31 participants revealed distinct trajectories between fixed-dose and dose-escalation strategies (Table 7C). In the fixed-dose subgroup (n=15), the OHA medication score decreased significantly from 1.16 ± 1.21 at baseline to 0.37 ± 0.34 at week 8 ($p<0.05$), alongside reductions in total daily insulin exposure (e.g., degludec lowered from 40 units at baseline to 25 units at week 8, and aspart reduced from 90 units to 30 units). This group also demonstrated greater adherence to structured LSM protocols, which likely potentiated pharmacological effects and

facilitated more pronounced regimen simplification. By contrast, the dose-escalation subgroup (n=16) had higher baseline medication scores (1.68 ± 1.29) and more complex insulin regimens, including combined degludec+aspart 70/30 mixes or mixed insulin formulations. While this group also achieved reductions (1.68 at baseline to 0.88 ± 1.10 at week 8, $p<0.01$), the relative decline was less steep, reflecting greater initial therapeutic intensity.

Table 7C: Changes in Medication Score (OHA and Insulin Regimen Adjustments) Over Time in Fixed-Dose and Dose-Escalation Groups (n=31)

Group	Time points	Medscore (OHA)	Insulin Regimen Adjustment
Fixed Dose (n=15)	At start of study	1.16 ± 1.21	Degludec 40 U + Aspart 90 U + Glargine 25 U
	Week 4	0.86 ± 1.14 ($p<0.01$)	30 units Degludec and 75 Units Aspart/Glargine 25 U
	Week 8	0.37 ± 0.34 ($p<0.05$)	Degludec 25 U + Aspart 30 U + Glargine 15 U
Dose escalation (n=16)	At start of study	1.68 ± 1.29	Degludec + Aspart 70/30 (62 U)/ Mixed insulin (72 U), Glargine (30 U)
	Week 4	1.06 ± 1.08 ($p<0.01$)	Degludec + Aspart 56 U, Glargine 5 U, Lispro 12 U
	Week 8	0.88 ± 1.1 ($p<0.01$)	Degludec + Aspart 56 U, Glargine 5 U, Lispro 12 U

In the dose-escalation group, insulin requirements declined across multiple classes. Within this group, insulin requirements declined significantly by week 4 and 8 ($p<0.01$ for both time points). Premixed insulin degludec + aspart 70/30 was reduced from 62 units to 56 units, mixed insulin was tapered from 72 units to complete discontinuation, and basal glargine was decreased from 30 units to 5 units. To fine-tune postprandial glycemic control, rapid-acting lispro was introduced at 12 units in selected participants, reflecting a more physiologic and simplified regimen. These adjustments illustrate statistically significant pharmacologic de-intensification accompanying tirzepatide therapy, whose dual GIP/GLP-1 receptor agonism promotes glucose-dependent insulin secretion, suppresses glucagon, and enhances insulin sensitivity. The observed reductions were further reinforced by personalized, tailored dietary/fitness interventions, which acted synergistically to reduce reliance on exogenous insulin.

Overall, these findings highlight that reductions in medication score and insulin requirements (all $p<0.05$ or $p<0.01$ across time points) were exhibited due to the insulin-sparing effect of tirzepatide, strengthened by structured diet and exercise interventions under LSM. The dual approach addressing both pharmacological drivers of glycemic control and lifestyle determinants of insulin resistance, resulted in meaningful simplification of regimens, reduced therapeutic complexity, and improved feasibility for longer-term diabetes management.

6. Discussion

This real-world evaluation of tirzepatide in adults with T2D underscores the drug's robust, dose-dependent efficacy and favorable tolerability profile, particularly when paired with structured, multidisciplinary lifestyle modification interventions. Tirzepatide's dual GIP and GLP-1 receptor agonism leverages multiple mechanistic pathways, not only enhancing insulin secretion and suppressing glucagon, but also promoting satiety and reducing central adiposity. These pharmacodynamic attributes are potentiated by the concurrent implementation of expert-guided dietary, fitness, and behavioral strategies, producing synergistic improvements in both metabolic and anthropometric outcomes.

The observed dose-dependent effects are clinically compelling. Patients maintained on a fixed 2.5 mg dose experienced appreciable, but modest, reductions in body weight (3.84 ± 1.94 kg, $p<0.001$), fasting blood glucose (24.42 ± 17.24 mg/dL, $p<0.001$), and postprandial glycemia (45.37 ± 35.60 mg/dL, $p<0.05$) over eight weeks. Dose escalation to 5 mg, in contrast, yielded significantly greater reductions in weight (5.22 ± 3.63 kg, $p<0.001$) and glycemic indices (26.87 ± 19.56 ($p<0.001$) and 54.29 ± 26.07 mg/dL ($p<0.001$) for FBS and PPBS, respectively), clearly delineating a pharmacological gradient of benefit. These results are notable even in the context of rigorous comparator trials. Remarkably, our short-term, real-world weight loss magnitude exceeds that of longer-duration studies such as the Adamidis et al. (Cureus, 2025) [67], SURPASS-2 [68], SURPASS-AP-Combo trial [69], and J.P. Frias et. al., [70] (**Table 8A**).

Table 8A: Comparative Evidence on Weight Reduction with Tirzepatide (5 mg) Across Clinical and Real-World Studies

Study	Study type	Tirzepatide Dose	Duration	Weight Loss (kg)
Adamidis et. al. [67]	Prospective observational study	5 mg	5 months	4
SURPASS-2 [68]	RCT	5 mg	52 weeks	3.7
SURPASS-AP-Combo [69]	Multi-arm RCT trial	5 mg	40 weeks	5
Frias JP et. al. [70]	RCT	5 mg	26 weeks	4.8
Our Current study	Retrospective	5 mg	8 weeks	5.22 ± 3.63

When extending the comparison to other approved GLP-1 receptor agonists, tirzepatide demonstrates both a greater magnitude and a more rapid onset of weight reduction. For instance, dulaglutide at 1.5 mg over 26 weeks achieved a mean weight loss of only 2.7 kg in the Frias JP et al. randomized controlled trial [70], while liraglutide at 1.8 mg over 56 weeks produced a 5.0 kg reduction in the SCALE Diabetes trial [71] (**Table 8B**). The ability of tirzepatide to induce comparable or superior weight loss within a substantially shorter treatment window highlights its emerging therapeutic advantage and supports its integration in comprehensive weight and glycemic management strategies.

Table 8B: Comparative Evidence on Weight Reduction with Tirzepatide (5 mg) Across Clinical and Real-World Studies

Study	Study type	Dose	Duration	Weight Loss (kg)
Frias JP et. al. [70]	RCT	1.5 mg dulaglutide	26 weeks	2.7
SCALE Diabetes randomized clinical trial [71]	RCT	1.8 mg liraglutide	56 weeks	5

Moreover, the overall medication burden, as assessed by longitudinal medication scores, demonstrated a significant attenuation over the study period. In the full cohort (n=41), a 34.34% reduction in medication score was observed, reflecting meaningful de-intensification alongside improved metabolic control. This effect was especially pronounced in the dose-escalation subgroup (n=31), which exhibited a 54.78% reduction in medication score, underscoring the enhanced benefits of titrated tirzepatide dosing. The most pronounced reduction was observed in the dose-escalation arm, where scores decreased from 1.68 ± 1.29 at initiation to 0.88 ± 1.10 ($p<0.01$) by week 8, whereas the fixed-dose 2.5 mg group showed a decrease from 1.16 ± 1.21 to 0.37 ± 0.34 ($p<0.01$) over the same interval, reflecting improvements in glycemic control but also illustrating a meaningful de-intensification of oral hypoglycemic agents alongside adjustments in insulin regimens.

Focusing on insulin regimens specifically, patients on fixed-dose tirzepatide (2.5 mg) commenced therapy with an aggregate total daily insulin dose of approximately 155 units. This comprised ultra-long-acting basal insulin (40 units), rapid-acting prandial insulin (90 units), and long-acting basal insulin (25 units). By week 8, total insulin requirements notably decreased to 70 units daily, reflecting reductions in each class: ultra-long-acting basal insulin to 25 units, rapid-acting prandial insulin to 30 units, and long-acting basal insulin to 15 units. In parallel, the dose-escalation group (2.5 mg escalating to 5 mg) started with a higher baseline aggregate of approximately 164 units per day. This included premixed insulin (~62 units), mixed insulin (72 units), and long-acting basal insulin (30 units). By week 8, insulin doses were significantly reduced to 73 units in total, involving premixed insulin reduced to 56 units, long-acting basal insulin to 5 units, and rapid-acting prandial insulin (lispro) to 12 units. These findings collectively demonstrate substantial insulin de-intensification that aligns with improved metabolic control under tirzepatide treatment, further enhanced by continuous, structured lifestyle modification support.

Furthermore, safety analyses are in line with, and in some regards surpass, established benchmarks for incretin-based therapies. Gastrointestinal adverse effects were commonly observed but typically transient and of mild-to-moderate severity, declining from 56.1% at week 4 to 48.4% by week 8 in the overarching cohort, while the proportion of participants reporting no side effects increased from 43.9% at week 4 to 51.6% by week 8. Notably, no patients discontinued therapy due to these side effects, reflecting high patient adherence and acceptability. The comparatively lower incidence of gastrointestinal disturbances in the present cohort, relative to the higher rates reported in the SURMOUNT trials (upto 72.8%) [72] and SURPASS-AP-Combo trial (upto 95%) [69] may be attributable to the rigorous protocolized dose escalation and robust multidisciplinary support framework, which included comprehensive patient education and close clinical monitoring. No instances of serious adverse events or hypoglycemic episodes occurred in either the fixed-dose or dose-escalation groups, highlighting the robust safety and tolerability of tirzepatide within this real-world clinical cohort. Notably, benefits were sustained even among individuals who temporarily paused tirzepatide during intercurrent illness or dose interruption, with no added risk of gastrointestinal or hypoglycemic events. Patients adhering strictly to lifestyle interventions demonstrated lasting impact despite missed doses, underscoring the durability of combined therapy. This finding reinforces the favorable safety profile observed in prior clinical trials and supports the use of tirzepatide alongside comprehensive lifestyle interventions and pharmacologic de-escalation strategies.

Strengths of the study include its integration of a real-world clinical setting, structured LSM, and comprehensive medication de-escalation strategy. The multi-pronged intervention, delivered by a coordinated team of physicians, health coaches, and behavioral experts, underscores the translational potential of tirzepatide therapy when deployed in a manner reflecting actual patient care. The use of a detailed medication scoring system allows not only quantification of metabolic efficacy but also a rigorous assessment of pharmacotherapy simplification, a key desideratum in contemporary diabetes management.

Nevertheless, limitations must be recognized. The study design was non-randomized and retrospective, leading to the potential for selection bias and uncontrolled confounding. The relatively short duration (8 weeks) restricts assertions regarding the durability of effect, long-term safety, and sustainability of pharmacologic de-escalation. The sample size, though adequate for early efficacy and safety signals, may underpower the detection of rare adverse outcomes and limit the granularity in subgroup analyses. Additionally, as the intervention was intensely supported and monitored, generalizability to broader populations with less access to integrated care pathways warrants further study.

In summary, tirzepatide, in conjunction with structured lifestyle intervention, demonstrates rapid, dose-dependent improvements in weight, glycemic control, and medication burden in patients with T2D, with a manageable safety profile. Further research should focus on long-term outcomes, the durability of de-intensification, and its applicability across diverse clinical settings.

7. Conclusion

This real-world evaluation of tirzepatide therapy adjunctive to structured lifestyle modification demonstrated clinically significant, dose-dependent improvements in anthropometric and glycemic parameters in adults with T2D complicated by overweight or obesity. Over eight weeks, tirzepatide's dual GIP and GLP-1 receptor agonism contributed to meaningful reductions in body weight, BMI, fasting blood sugar, and postprandial glucose, accompanied by decreases in waist circumference, highlighting its multifaceted impact on core pathophysiological mechanisms including pancreatic β-cell

function, appetite regulation, glucagon suppression, and adipocyte metabolism.

Subgroup analyses showed distinct mechanistic effects by dose: participants maintained on 2.5 mg benefited primarily from enhanced insulin secretion and moderate satiety effects yielding moderate weight loss and glycemic control, whereas dose escalation to 5 mg elicited greater incretin receptor engagement resulting in more pronounced appetite suppression, adipocyte lipolysis, and insulin sensitivity. These metabolic effects were supported by comprehensive multidisciplinary care through the SugarFit program, encompassing tailored dietary, fitness, and behavioral interventions alongside continuous clinical monitoring, which facilitated medication burden reduction, minimized adverse events, and optimized adherence.

Although adverse events with tirzepatide are relatively common, their severity and impact were mitigated by the intensive support provided through the program, enabling safe dose titration and progressive medication de-intensification. Tirzepatide's once-weekly dosing further enhances patient compliance and treatment persistence, key factors in achieving optimal glycemic control and weight management. Together, these findings underscore tirzepatide combined with expert-guided lifestyle interventions as an effective therapeutic strategy for managing T2D with concomitant obesity in real-world clinical practice. Nonetheless, longer-term studies across diverse populations are needed to confirm sustained safety, effectiveness, and improvements in overall quality of life and treatment adherence.

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