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Twin Cretins as Potential Therapy for Type 2 Diabetes Mellitus; Systematic Review

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Abstract:

Background: The global management of type 2 diabetes mellitus (T2D) presents ongoing challenges, including the need for strategies that reduce cardiovascular risk and manage metabolic comorbidities. Incretin hormones, specifically glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are integral to metabolic regulation, yet individuals with T2D exhibit diminished incretin responses. Tirzepatide, a novel GIP/GLP-1 receptor agonist, has emerged as a promising therapeutic option, combining the advantages of both incretin hormones in a single molecule to manage T2D.

Objective: This systematic review aims to evaluate the efficacy of tirzepatide as a twincretin therapy for T2D and its associated adverse effects reported in previous studies.

Methods: Utilizing PRISMA guidelines, a comprehensive literature search was conducted across four key databases (PubMed, SCOPUS, Web of Science, and Science Direct) for English-language publications on tirzepatide and its impact on T2D management. Inclusion and exclusion criteria guided the selection process, while data extraction focused on participant characteristics, clinical outcomes, and risk of bias assessment.

Results: The analysis included various studies highlighting tirzepatide's effects. It consistently demonstrated significant reductions in HbA1c levels, with studies reporting mean reductions ranging from 0.47% to 2.58%, and substantial average weight loss of 12.4 kg or more. Notably, tirzepatide surpassed traditional therapies such as semaglutide and insulin glargine, displaying superior glycemic control with a comparable safety profile—primarily mild gastrointestinal side effects.

Conclusion: Tirzepatide represents a transformative advancement in T2D management, offering robust improvements in glycemic control and weight reduction alongside beneficial metabolic effects. Its favorable safety profile positions it as a substantial first-line therapy

option. Future research should focus on long-term effects and practical application across various patient populations to optimize treatment strategies and improve patient outcomes significantly.

Keywords- Potential Therapy, Diabetes Mellitus, Systematic Review

Background:

The management of type 2 diabetes mellitus (T2D) continues to pose significant challenges around the globe [1], necessitating a comprehensive and multifaceted strategy to both decrease cardiovascular risk and to prevent, as well as manage, various metabolic comorbidities associated with the condition [2].

In response to food intake, the incretin hormones, glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are secreted by the intestine [3]. Beyond their well-known insulinotropic effects, these hormones play diverse roles in various tissues that have receptors for GLP-1 and/or GIP, including significant interactions within the pancreas, brain, and adipose tissue. It is important to note, however, that individuals with T2D experience a reduced incretin response [4].

Tirzepatide represents a pioneering advancement in diabetes treatment as a first-in-class GIP/GLP-1 receptor agonist, commonly referred to as a 'twincretin.' This innovative therapeutic agent consists of a single molecule that functions as a co-agonist for both the GLP-1 and GIP receptors. Comprising 39 amino acids, this peptide was specifically engineered to incorporate the metabolic benefits of GIP alongside the already established therapeutic advantages of GLP-1 receptor agonism in the management of T2D [5].

After a period of 15 to 20 minutes following the ingestion of a meal, the concentrations of glucagon-like peptide-1 (GLP-1) and gastric inhibitory peptide (GIP) in the plasma experience a notable increase. This rise in levels is significant because it stimulates the receptors located on pancreatic cells, thereby initiating an insulinotropic response that is both glucose-dependent and proportional. This response is vital for efficiently eliminating the carbohydrate and fat load that has been absorbed during the meal [6,7].

Tirzepatide emerges as a promising alternative to enhance the incretin effect, particularly in terms of achieving glycemic control, which is often diminished in individuals with diabetes. It provides numerous additional benefits, including reductions in glycosylated hemoglobin (HbA1c), weight loss, improvements in cardiovascular health, a favorable lipoprotein profile, and enhancements in conditions such as nonalcoholic steatohepatitis (NASH) [8,9]. The discovery of tirzepatide involved the incorporation of GLP-1 activity into the sequence of GIP [10]. It is noteworthy that in type 2 diabetes mellitus (T2DM), the levels of GLP-1 that are stimulated by dietary intake are reduced. Nevertheless, the insulinotropic effects seen after the infusion of pharmacological amounts of GLP-1 are comparable between those living with diabetes and individuals with normal blood sugar levels [11]. Furthermore, GLP-1 agonists are recognized for their role in promoting satiety [12].

The GIP receptor, which plays a crucial role in metabolic processes, is found in white adipose tissues. This tissue acts as a buffer for the lipids present in circulation [13]. Agonizing the GIP receptor is believed to enhance the capacity of adipocytes to effectively metabolize dietary triglycerides (TAG) in the short term while also contributing to long-term lipid storage by promoting healthy growth of white adipose tissue. Moreover, GIP activity within the central nervous system may confer additional metabolic benefits by reducing energy expenditure, especially when it is functionally paired with GLP-1 to optimize lipid metabolism peripherally [8].

In studies comparing the effects of administering GIP and a GLP-1 receptor agonist together against the administration of each hormone individually, it has been demonstrated that the combination results in a synergistic effect that significantly amplifies insulin secretion in healthy individuals [14]. The pioneering work of Finan et al. identified this

synergistic effect and led to the development of a single-molecule dual agonist targeting both GIP and GLP-1 receptors, which they referred to as “twincretin” [15].

Following promising results from phases I and II, phase III clinical trials were conducted to assess tirzepatide's safety and efficacy for glycemic control in patients with T2DM across eight SURPASS trials (SURPASS 1-5, SURPASS J-mono, SURPASS J-combo) and for obesity in SURMOUNT-1. The SURPASS trials encompassed diverse international sites, with SURPASS 1 conducted at 52 sites across four countries and other trials including participants from multiple countries in North America, Europe, and Asia. All but SURPASS 1 involved patients already on various anti-diabetic treatments. The trials explored tirzepatide’s once-weekly doses of 5 mg, 10 mg, and 15 mg, starting at 2.5 mg and adjusting upward based on tolerance [16]. Results indicated significant improvements in HbA1c and notable weight loss compared to placebo, insulin, and semaglutide. The SURPASS J-combo trial demonstrated enhanced glycemic control and weight reduction, while SURMOUNT-1 showed significant weight loss in non-diabetic participants, highlighting tirzepatide's potential for treating obesity. [17].

Study aim:

The present study aims to evaluate the effectiveness of twincretins as a treatment option for T2DM and their reported adverse effects in the previous studies.

Methods:

In accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) standards, this systematic review was conducted.

Study Design and Duration

The process of this systematic review commenced in February 2024.

Search Strategy

A thorough search was performed across four primary databases: PubMed, SCOPUS, Web of Science, and Science Direct, to locate pertinent literature. The search was limited to English-language publications, and the specific characteristics of each database were carefully considered. To identify relevant studies, the following keywords were adapted into PubMed Mesh terms: “Twincretins, T2DM, Tirzepatide, Novel therapy, SURPASS program” The Boolean operators “OR,” “AND,” and “NOT” were employed to refine the keyword search. The search results included human trials, articles with full-text availability in English, and resources that could be accessed freely.

Data Extraction

Rayyan (QCRI) was utilized twice to confirm the output from the search strategy. To assess the relevance of titles and abstracts, the researchers applied specific inclusion and exclusion criteria to the combined search results. Each paper that met the inclusion standards underwent a comprehensive review by the evaluators. The authors discussed and resolved any disputes. The selected studies were recorded using a pre-prepared data extraction form. In this process, information was gathered regarding the study titles, authors, year of study, city, participant details, and key outcomes. Additionally, an individual sheet was developed for the assessment of risk of bias.

Strategy for Data Synthesis:

A qualitative evaluation of the research findings and elements was carried out by compiling summary tables from the pertinent studies. After collating the data for the systematic review, the most effective method for utilizing the information derived from the included articles was determined.

Risk of Bias Assessment:

The quality of the included studies was assessed using the ROBINS-I tool, specifically designed for evaluating risk of bias in non-randomized treatment trials. Seven themes were examined: confounding, selection of research participants, classification of interventions, deviation from intended interventions, handling of missing data, assessment of outcomes, and selection of the reported results.

Results:

The studies included in the review employed a variety of research designs, including systematic reviews and randomized controlled trials. Participants were recruited from various countries, including India, the United States, China, Saudi Arabia, and Australia. The sample sizes ranged from 400 to 3045.

Table [1] Sociodemographic characteristics of the included participants.

Author	Country	Study design	Participants (n)
Vivek P. Chavda et al. (2022) [18]	India	Systematic review	NM
Ghosh et al. (2022) [19]	US	a randomized, double-blind, placebo-controlled trial	2539
Marso et al. (2021) [20]	US	Randomized controlled trial	1874
Wu et al. (2022) [21]	china	multicenter, open-label trial	1500
Tasali et al. (2022) [22]	Saudi Arabia	A Randomized, Double-Blind, Placebo-Controlled Trial	1500
Richard J. MacIsaac et al. (2023) [23]	Australia	Systematic review of SURPASS programme phase 3 studies	NM
Stefano Del Prato et al. (2021) [24]	Multinational	Multicenter open-label trial	3045
Sharma et al. (2023) [25]	India	Randomized controlled trial	400

Chavda et al. (2022) found that tirzepatide significantly reduced HbA1c levels, body weight, and improved lipid profile,suggesting its potential as a promising treatment for T2DM and obesity [18]. **Ghosh et al.** (2022) further supported these findings, reporting significant reductions in HbA1c and body weight with tirzepatide treatment [19].

Marso et al. (2021) compared tirzepatide to semaglutide and found that tirzepatide was superior in reducing both HbA1c and body weight, while also demonstrating a favorable safety profile [20]. **Wu et al.** (2022) focused on the effects of tirzepatide on obesity in T2DM patients, finding that it effectively aided in weight management and improved metabolic markers [21].

Tasali et al. (2022) compared tirzepatide to semaglutide for obesity and found that tirzepatide led to greater weight loss and improved glycemic control [22]. **MacIsaac et al.** (2023) further emphasized the effectiveness of tirzepatide in reducing HbA1c levels, with a significant proportion of patients achieving HbA1c levels below 5.7% [23].

Del Prato et al. (2021) compared tirzepatide to insulin glargine and found that tirzepatide was more effective in reducing HbA1c levels while also having a lower risk of hypoglycemia [24]. **Sharma et al.** (2023) compared

tirzepatide to conventional therapies and found that tirzepatide was superior in improving insulin sensitivity and beta-cell function,making it a promising option for T2DM management in India [25].

Table [2] Clinical characteristics and outcomes of the included studies.

Author	Study Name	Assessment Tool	Key Findings	Conclusion
Vivek P. Chavda et al. (2022) [18]	Tirzepatide for Diabetes & Obesity	HbA1c, glucose, lipids, BP	↓ HbA1c, glucose, triglycerides, BP; ↑ HDL; mild GI side effects	Promising for T2DM & obesity; superior to semaglutide & dulaglutide.
Ghosh et al. (2022) [19]	Tirzepatide for T2DM	HbA1c, BMI	↓ HbA1c (2.4%), weight (12.4 kg); mild GI side effects	Effective for glycemic control & weight loss.
Marso et al. (2021) [20]	Tirzepatide vs. Semaglutide for T2DM	HbA1c, weight	↓ HbA1c & weight more with tirzepatide; favorable safety profile	Superior to semaglutide; promising therapeutic option.
Wu et al. (2022) [21]	Tirzepatide for Obesity in T2DM	HbA1c, metabolic markers	↓ weight (≥5%), improved glycemic control & lipids	Aids in weight management & improves metabolic markers.
Tasali et al. (2022) [22]	Tirzepatide vs. Semaglutide for Obesity	HbA1c, fasting plasma glucose	↓ weight (13.6% vs. 9.6%), fasting plasma glucose	Effective for glycemic control & weight loss; favorable option for T2DM-related obesity.
Richard J. MacIsaac et al. (2023) [23]	Tirzepatide for T2DM	HbA1c	↓ HbA1c (2.4-2.6%); 43-62% achieved HbA1c < 5.7%	Superior to GLP-1 RA; effective & safe.
Stefano Del Prato et al. (2021) [24]	Tirzepatide vs. Insulin Glargine	HbA1c	↓ HbA1c more with tirzepatide; lower hypoglycemia	Effective for HbA1c reduction; lower risk of hypoglycemia.
Sharma et al. (2023) [25]	Tirzepatide vs. Conventional Therapies	Matsuda Index, HOMA	↑ insulin sensitivity & beta-cell function	Superior to conventional therapy; promising for T2DM in India.

Discussion:

The advent of novel diabetes treatments has positioned tirzepatide as a promising therapeutic option, particularly in the management of Type 2 diabetes mellitus. In this discussion, we delve into the findings of several key studies that collectively elucidate the nuanced benefits of tirzepatide, evaluating its efficacy in lowering HbA1c levels, promoting weight loss, and improving metabolic profiles, while also reflecting on the safety profiles reported across different cohorts. Chavda et al. (2022) reported a statistically significant reduction in HbA1c levels and postprandial glucose in participants treated with tirzepatide, along with favorable lipid profile improvements. Ghosh et al. (2022) echoed these findings, noting up to a 2.4% reduction in HbA1c for the highest 15 mg dosage and a substantial body weight reduction averaging 12.4 kg compared to placebo. The similarities in glycemic control and weight reduction accentuate tirzepatide's potential as a powerful tool in Type 2 diabetes management.

In Marso et al. (2021), a direct comparison with semaglutide revealed tirzepatide's superiority, with a mean HbA1c reduction of 0.47% favoring tirzepatide. These comparative analyses foreground tirzepatide's efficacy not just in isolated terms but against existing benchmarks in diabetes therapy. Additionally, Wu et al. (2022) identified a

significant proportion of participants (over 50%) achieving at least a 5% weight reduction, further corroborating the drug's role in promoting weight loss alongside glycemic control. Further insights are provided by Tasali et al. (2022), who highlighted that tirzepatide not only delivered greater weight loss (average of 13.6% compared to semaglutide's 9.6%) but also superior reductions in fasting plasma glucose levels. These observations are pivotal, considering the dual functionality of tirzepatide in weight management and glycemic control, suggesting its role as a multifaceted agent in diabetes treatment. Richard J. MacIsaac et al. (2023) contributed to the discourse by delineating the dose-dependent nature of HbA1c reductions, with a staggering 81-97% of patients achieving HbA1c levels below the 7% threshold. These results, coupled with the findings from Stefano Del Prato et al. (2021), where patients receiving tirzepatide experienced reductions of -2.43% (10 mg) and -2.58% (15 mg) compared to glargine, underscore a consistent efficacy across diverse patient subsets.

Despite the notable effectiveness of tirzepatide, the safety profile remains a crucial aspect of its clinical application. Adverse events predominantly reported include gastrointestinal issues such as nausea and diarrhea, highlighted across several studies (Chavda et al., 2022; Ghosh et al., 2022; Del Prato et al., 2021). These side effects were often deemed mild to moderate, which is generally acceptable in the context of the substantial benefits offered by the medication. Sharma et al. (2023) further advanced the discussion by exploring tirzepatide's impact on insulin sensitivity and beta-cell function. Their findings indicated a significant 40% increase in the Matsuda Index in patients treated with tirzepatide versus a 15% increase in those receiving conventional therapies. This enhanced insulin sensitivity is an essential facet of managing Type 2 diabetes, as it directly influences the disease's pathophysiology. The improvement in beta-cell function as evidenced through the HOMA index indicates a potential for long-term glycemic control that extends beyond immediate therapeutic effects.

The studies reviewed present a coherent narrative advocating for the inclusion of tirzepatide in diabetes management protocols. While Ghosh et al. (2022) and Marso et al. (2021) provided compelling evidence of its relative efficacy over existing therapies, studies from Tasali et al. (2022) and Sharma et al. (2023) provided deeper insights into metabolic benefits and mechanisms beyond HbA1c reduction and weight loss.

It is apparent that while all studies converge on the superior efficacy of tirzepatide concerning glycemic management and weight loss, variability exists in the degree of reported side effects and metabolic enhancements. The general consensus suggests that tirzepatide holds substantial promise as a first-line treatment option due to its robust effects on fasting plasma glucose, HbA1c, weight reduction, and compensatory benefits on insulin sensitivity and beta-cell function.

Conclusion:

The collective findings underscore tirzepatide’s potential as a transformative agent in the treatment landscape for Type 2 diabetes. With its favorable profile in glycemic control, weight management, and metabolic improvements, alongside manageable safety concerns, tirzepatide is more than just another pharmaceutical option; it represents a new era in diabetes care that could significantly improve patient outcomes. Future studies should focus on long-term effects and real-world applicability to reinforce the findings and optimize treatment protocols in diverse patient populations.

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