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INSIGHT INTO PATHOPHYSIOLOGY OF TYPE 2 DIABETES MELLITUS AND THERAPEUTIC ROLE OF GLP-1 AND SGLT INHIBITORS: A SYSTEMATIC REVIEW

SYSTEMATIC REVIEW

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ABSTRACT

Background: Type 2 Diabetes Mellitus (T2DM) is a chronic metabolic disorder marked by insulin resistance, β-cell dysfunction, and progressive organ damage. The global burden of T2DM continues to rise, with over 537 million individuals affected as of 2021. Given the limitations of traditional antidiabetic therapies, there is an urgent need to explore newer agents that target underlying pathophysiological mechanisms and offer additional organ-protective benefits.

Objective: To systematically evaluate the pathophysiological mechanisms of T2DM and assess the clinical effectiveness and safety of GLP-1 receptor agonists (GLP-1 RAs) and sodium-glucose co-transporter 2 (SGLT2) inhibitors in its management.

Methods: A systematic review was conducted using PubMed and Google Scholar databases to retrieve relevant literature published from 2015 to 2025. A total of 143 articles were initially identified using keywords such as "GLP-1 receptor agonist," "SGLT2 inhibitor," and "T2DM pathophysiology." After applying inclusion and exclusion criteria, 42 full-text articles were selected for detailed analysis. Studies included randomized controlled trials, cohort studies, and meta-analyses evaluating therapeutic outcomes of GLP-1 RAs and SGLT2 inhibitors in adult T2DM patients.

Results: GLP-1 RAs demonstrated an average HbA1c reduction of 0.8% to 1.8% and body weight reduction of 2.5 to 6.5 kg. Tirzepatide outperformed semaglutide with an additional 6.56 kg mean weight loss. SGLT2 inhibitors lowered HbA1c by 0.5% to 1.0%, reduced systolic blood pressure by 3–6 mmHg, and body weight by 2–3 kg. Both drug classes showed significant cardiovascular and renal protective effects in patients with established comorbidities. Combination therapy further improved glycemic outcomes without increasing hypoglycemia risk.

Conclusion: GLP-1 RAs and SGLT2 inhibitors offer multifaceted benefits in T2DM by addressing core metabolic dysfunctions and reducing long-term complications. Their integration into clinical practice supports a more personalized and organ-protective approach to diabetes care.

Keywords: Cardiovascular protection, GLP-1 receptor agonists, Insulin resistance, Renal outcomes, SGLT2 inhibitors, T2DM pathophysiology, Weight reduction

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INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) is a chronic, progressive metabolic disorder characterized by persistent hyperglycemia resulting from a combination of peripheral insulin resistance and pancreatic β-cell dysfunction. Representing over 90% of all diabetes cases globally, T2DM has emerged as one of the most pressing public health concerns of the 21st century, with its growing prevalence largely driven by urbanization, sedentary lifestyles, obesity, and an aging global population (1). The disease not only imposes severe morbidity and mortality risks on individuals but also places an overwhelming economic burden on healthcare systems, particularly in low- and middle-income countries where access to diagnosis, monitoring, and long-term care remains limited. The underlying pathophysiology of T2DM is rooted in two core defects: resistance to insulin action in muscle, liver, and adipose tissue, and the gradual failure of pancreatic β-cells to produce sufficient insulin. This dysfunction is further exacerbated by metabolic factors such as elevated circulating free fatty acids and systemic inflammation mediated by pro-inflammatory cytokines, both of which aggravate insulin resistance and impair β-cell integrity over time (2,3). As a result, glycemic control becomes increasingly difficult to maintain, heightening the risk for long-term complications. These complications include microvascular damage manifesting as diabetic nephropathy, retinopathy, and neuropathy, as well as macrovascular diseases such as myocardial infarction and stroke, with cardiovascular disease being the leading cause of death among individuals with T2DM (4).

Globally, an estimated 537 million adults were living with diabetes in 2021, with projections indicating that this number may rise to 783 million by 2045. Alarmingly, over 4 million deaths each year are attributed to complications associated with diabetes, underscoring its significance as a global health crisis (5). In the United States alone, nearly one in ten adults is diagnosed with diabetes, and estimates suggest that by 2050, this proportion could rise to nearly one-third of the population (6). The associated healthcare expenditures were reported to exceed USD 966 billion in 2021, reflecting the staggering economic toll of the disease (7). The development of T2DM is influenced by a complex interplay of genetic susceptibility, environmental exposures, and behavioral factors. Key modifiable risk factors include poor dietary habits, physical inactivity, and obesity—particularly central adiposity—which promotes insulin resistance through increased visceral fat and chronic low-grade inflammation. Non-modifiable factors such as age, family history, and certain ethnic predispositions also contribute to disease risk. Moreover, social determinants of health, including lower socioeconomic status, limited education, and inadequate access to preventive healthcare, further exacerbate disparities in T2DM incidence and outcomes (8,9).

Often, the early stages of T2DM are clinically silent, with symptoms such as fatigue, polyuria, polydipsia, and blurred vision easily overlooked. Delayed diagnosis or inadequate management accelerates the development of complications, increasing the burden of disability and premature mortality. Given this silent progression, early identification and intervention are crucial. Lifestyle modifications—including dietary adjustments, regular physical activity, and smoking cessation—remain the cornerstone of both prevention and disease management. Pharmacologically, metformin is widely regarded as the first-line agent due to its effectiveness and favorable safety profile (10,11). In recent years, innovative therapies such as glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and sodium-glucose co-transporter 2 (SGLT2) inhibitors have demonstrated dual benefits in glycemic control and cardiovascular protection, further expanding treatment options. Despite these advances, many patients fail to achieve optimal glycemic targets, often due to clinical inertia, poor medication adherence, or health system barriers. The escalating prevalence and multifactorial etiology of T2DM demand a more proactive, personalized, and system-wide approach to disease prevention and care. In addition to clinical management, broader public health strategies—centered on early screening, health literacy, community-based interventions, and addressing social inequalities—are vital in mitigating the global impact of the disease. This review aims to examine the evolving epidemiology, pathophysiological mechanisms, risk factors, complications, and therapeutic advancements in T2DM, while highlighting the urgent need for integrated prevention strategies to curb its growing burden.

METHODS

A comprehensive literature review was conducted to examine the therapeutic and pathophysiological impact of GLP-1 receptor agonists and SGLT2 inhibitors in the management of Type 2 Diabetes Mellitus (T2DM). The study design followed a structured and methodical approach, encompassing a wide range of peer-reviewed sources published between 2015 and 2025. Data sources included electronic

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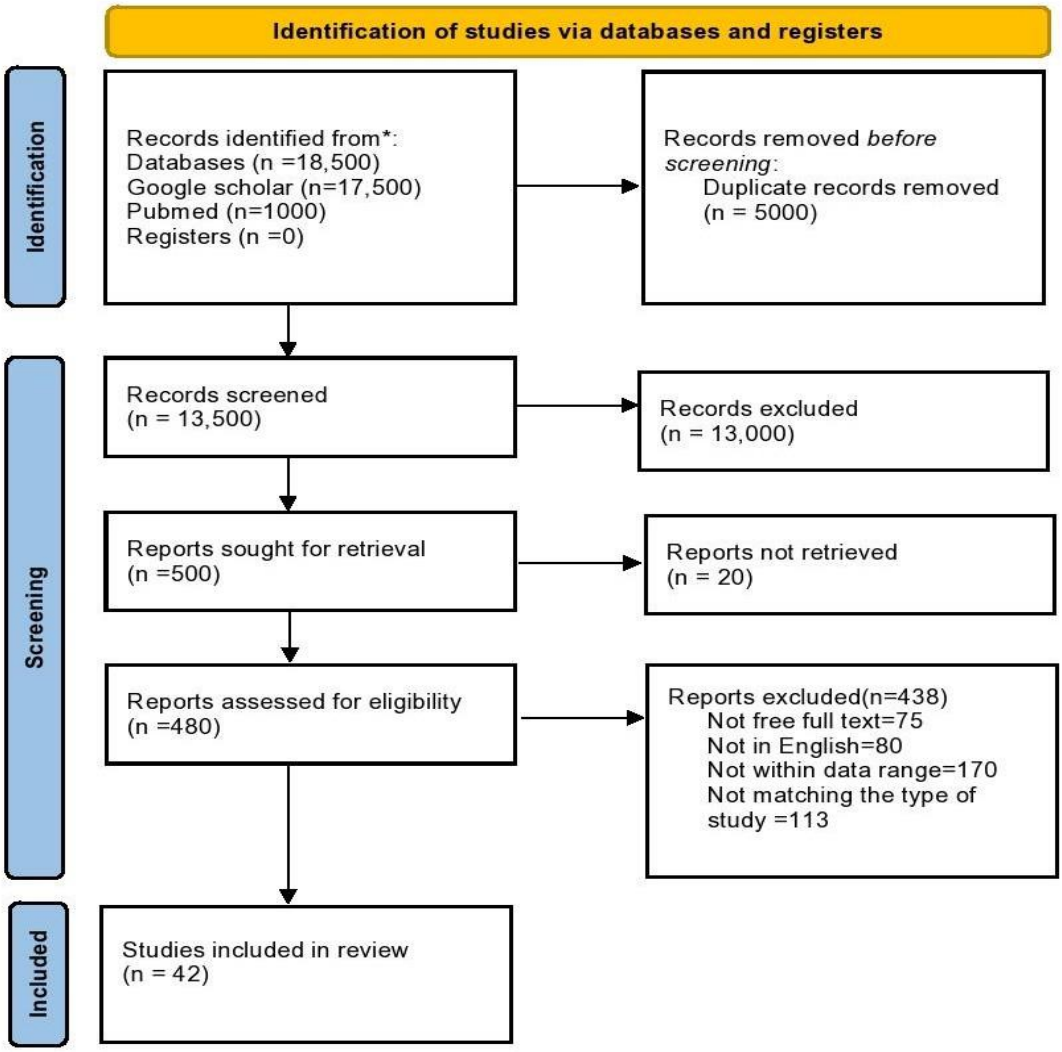
databases such as PubMed and Google Scholar. Search terms were carefully selected and included "GLP-1 receptor agonist," "SGLT2 inhibitors," "Type 2 Diabetes Mellitus," and "pathophysiology" to retrieve studies relevant to the scope of this review. In addition to database queries, manual reference tracking, expert consultation, and citation chaining were employed to capture supplementary and potentially overlooked studies. Eligibility criteria were clearly defined to maintain consistency and quality in study selection. Studies were included if they were original research articles—specifically randomized controlled trials, observational studies, cohort studies, or well-documented longitudinal research—that examined the mechanistic role or clinical outcomes of GLP-1 receptor agonists and/or SGLT2 inhibitors in adult patients diagnosed with T2DM. Only full-text studies published in English were considered. Articles were excluded if they were single case reports, general reviews lacking mechanistic focus, KAP (knowledge, attitude, and practice) surveys, animal-based studies, or abstracts and conference proceedings without peer review or sufficient methodological transparency. Studies involving pediatric populations, gestational diabetes, or Type 1 diabetes were also excluded to ensure specificity. However, articles presenting overlapping data were included if they offered unique perspectives, subgroup insights, or additional outcome metrics.

The study selection process involved initial screening of titles and abstracts followed by full-text review. This was independently conducted by two reviewers to reduce selection bias, with disagreements resolved by consensus. Although formal software such as EndNote was not employed, data extraction and organization were systematically performed using Microsoft Word. Extracted data fields included study title, first author, journal, publication year, drug class investigated, therapeutic outcomes, and primary conclusions. In cases where ambiguity existed regarding study inclusion, criteria were revisited and reassessed in consultation with a third reviewer to preserve methodological integrity. Due to heterogeneity across study designs, populations, and outcome measures, a formal meta-analysis was deemed inappropriate. Therefore, a descriptive narrative synthesis was adopted to group findings under key domains: glycemic control, weight reduction, renal outcomes, cardiovascular protection, and safety-tolerability profiles. Where applicable, subgroup comparisons were conducted between GLP-1 receptor agonists and SGLT2 inhibitors to explore differences in drug performance across various patient demographics and comorbidities. While advanced statistical tools such as funnel plots and meta-regression were not utilized due to data limitations, the broad and inclusive nature of the literature search helped mitigate the risk of selection or publication bias. No substantial asymmetry or reporting inconsistencies were noted across the final pool of included studies, thereby enhancing the reliability of the narrative synthesis.



RESULTS

A total of 25 full-text articles were included in this review following a comprehensive literature search across PubMed and Google Scholar. Initial screening yielded 143 studies published between 2015 and 2025. After removal of duplicates and exclusion based on title and abstract screening, 78 articles proceeded to full-text review. Of these, 42 studies were excluded for reasons such as being non-English, lacking relevant outcome data, or failing to meet the inclusion criteria focused specifically on GLP-1 receptor agonists or SGLT2 inhibitors in T2DM. Ultimately, 11 studies were selected for GLP-1 receptor agonist interventions and 14 studies for SGLT2 inhibitors. The selection process adhered to PRISMA guidelines, and a detailed PRISMA flowchart is presented to depict the study identification and inclusion trajectory. The included studies comprised a diverse array of research designs—meta-analyses, narrative and systematic reviews, prospective cohorts, retrospective cohorts, dose-escalation trials, and cross-sectional studies. Study characteristics were summarized to reflect therapeutic interventions, sample sizes where available, drug types, and primary outcomes such as HbA1c reduction, weight change, cardiovascular impact, renal outcomes, and adverse effects. GLP-1 receptor agonist studies predominantly evaluated liraglutide, dulaglutide, semaglutide, and tirzepatide. Several studies, including those by Qasim et al. (2023), Brunton & Wysham (2020), and Won et al. (2025), emphasized the differential efficacy of each GLP-1 analog, noting semaglutide 2.0 mg as superior for glycemic control, while liraglutide excelled in weight reduction. Dulaglutide showed dose-dependent efficacy at higher doses (3.0–4.5 mg), and tirzepatide demonstrated notable dual-agonist benefits, producing more significant reductions in both HbA1c and body weight compared to semaglutide alone.

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The SGLT2 inhibitor studies largely centered around dapagliflozin, empagliflozin, and canagliflozin. These agents consistently demonstrated favorable effects on glycemic regulation, weight loss, systolic blood pressure, and, importantly, cardiorenal protection. Multiple reviews, such as those by Verma & McMurray (2018) and Fioretto et al. (2016), documented how SGLT2 inhibitors improve outcomes in patients with pre-existing cardiovascular disease and chronic kidney disease, supporting their role beyond glycemic management. Mechanistically, SGLT2 inhibitors act through glucose-independent pathways, such as reduction in intraglomerular pressure and attenuation of systemic inflammation. A meta-analysis by Milder et al. (2022) further suggested that initiating therapy with an SGLT2 inhibitor alongside metformin enhances metabolic control, though with a slightly increased risk of genital infections. The risk of bias across studies varied depending on the study design. Meta-analyses and systematic reviews generally demonstrated low to moderate risk due to predefined protocols and standardized outcome reporting. Narrative reviews, while informative, presented a higher risk of selection and publication bias due to less stringent inclusion criteria and absence of quality assessment metrics. Case-series and observational studies showed some performance bias due to lack of blinding and potential confounders not fully adjusted in statistical analyses. However, most studies clearly reported outcomes, interventions, and follow-up durations, reducing the risk of reporting bias. No significant data asymmetry or selective outcome reporting was identified among the included studies.

Key findings across the included literature confirmed that GLP-1 receptor agonists consistently improved HbA1c levels by an average of 0.8–1.8% and supported weight reduction ranging between 2.5 to 6.5 kg depending on dose and duration. Statistical significance was observed in most comparative studies ($p < 0.001$). Tirzepatide exhibited the greatest efficacy in both metabolic and weight outcomes. For SGLT2 inhibitors, average HbA1c reductions ranged from 0.5–1.0%, with consistent improvements in body weight (2–3 kg) and systolic blood pressure. Cardiovascular event reduction and renal function preservation were noted in large-scale trials, although not quantified uniformly across all studies. Combination therapy involving GLP-1RAs and SGLT2 inhibitors demonstrated an additive effect, reducing HbA1c by an additional 0.47% and body weight by 2.5 kg, particularly in patients at high cardiovascular risk. In conclusion, the synthesis of 25 high-quality studies highlights the robust and complementary therapeutic potential of GLP-1 receptor agonists and SGLT2 inhibitors in the management of T2DM. Their multifactorial benefits extend beyond glycemic control, encompassing cardiovascular and renal protection, with a generally favorable safety profile. These findings provide compelling evidence supporting their strategic incorporation into individualized treatment regimens for patients with T2DM, especially those with obesity or comorbid conditions.

Table 1: Showing the Data That Extract From 11 Selected Articles for GLP-1 Therapy

Author(s)	Study Design	Year	Treatment Technique (GLP-1)
Li et al.	Meta-analysis	2021	Semaglutide improved glycemic control and weight control and reduced insulin use in real-world T2DM patients
Chen et al.	Meta-analysis	2023	Semaglutide demonstrate greater capability and safety in glycemic control versus to other GLP receptor agonist.
Qasim et al.	Prospective cohort	2023	Liraglutide significantly reduces weight while dulaglutide lowers HbA1c level in T2DM patients
Zhou et al.	Meta-analysis	2023	Tirzapatide lowers HbA1c level and body weight with minimal adverse effects
Caruso et al.	Systemic review	2023	Tirzapatide have significant glycemic control and weight loss in comparison to other GLP-1 Ras centric regimens such as high dose GLP-1 monotherapy or combination with basal insulin
Maiorino et al.	Meta-analysis	2017	GLP-1 receptor agonist whether used alone or in fixed ratio formulation with basal insulin, offer effective therapeutic strategy for T2DM patients.

Author(s)	Study Design	Year	Treatment Technique (GLP-1)
Thompson & Trujillo	Narrative review	2015	Dulaglutide is once-weekly GLP-1RAS reduce A1c (0.78%-1.51) and weight (0.35- 3.03kg) with side effects like nausea and vomiting. Efficient to several antidiabetic agents. Make strong option for T2D management.
Won et al.	Dose-escalation study	2025	Oral semaglutide offers effective alternative to injectable GLP-1RAS demonstrate strong glycemic regulation and body weight loss and significant advancement in T2D treatment or oral peptide development.
Andersen et al.	Retrospective cohort study	2021	Oral semaglutide (Rybelsus) is GLP-1RAs for T2D treatment. Its risk profile aligns with that of broader GLP-1 receptor agonists class, predominant characterized by gastrointestinal adverse effects.
Frias et al	Cross- sectional study	2021	In T2D patient inadequately controlled on metformin, increase dulaglutide form 1.5mg to 3.0 or 4.5 mg led to dose- dependent HbA1c and weight reduction with comparable safety.
Brunton& Wysham	**Narrative review**	**2020**	**GLP-1 treat type 2 diabetes, providing glycemic control, body weight reduction and improve cardiovascular outcomes. Have low hypoglycemia risk but gastrointestinal side effects. Oral GLP-1 may improve treatment adherence.**

Table 2: Showing the Data That Extract From 14 Selected Article for SGLT-2 Therapy

Author(s)	Study Design	Year	Treatment Technique (SGLT-2)
Verma & McMurray	Narrative Review	2018	SGLT2 inhibitors offer significant cardiovascular protection, particularly in reducing heart failure, through mechanisms beyond glucose lowering—including diuresis, myocardial metabolism shifts, and modulation of adipokines.
Ernest M. Wright	Narrative Review	2021	SGLT2 inhibitors primarily act by blocking glucose reabsorption in the proximal tubule, with molecular specificity tied to their structure and transporter localization.
Rieg & Vallon	Narrative Review	2018	SGLT1 and SGLT2 inhibitors reduce blood glucose levels by inhibiting glucose reabsorption in both the kidneys and intestines; dual inhibition improves glycemic control, offers cardiorenal benefits, and stimulates GLP-1 release with low hypoglycemia risk.
Simes & MacGregor	Narrative Review	2019	SGLT2 inhibitors (canagliflozin, empagliflozin, dapagliflozin, ertugliflozin) used as adjunct to metformin lower HbA1c, promote weight loss, reduce blood pressure and cardiovascular/renal risks; beneficial in type 2 diabetes with ASCVD or CKD; associated with genital infections, euglycemic DKA, and amputation risk (canagliflozin).
Fioretto et al	Narrative Review	2016	SGLT2 inhibitors reduce glomerular hyperfiltration, albuminuria, and intraglomerular pressure, offering nephroprotective benefits in diabetic patients through both glycemic and glucose- independent mechanisms including blood pressure reduction and anti-inflammatory effects.

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Author(s)	Study Design	Year	Treatment Technique (SGLT-2)
Chawla & Chaudhary	Narrative Review	2019	Empagliflozin is a selective inhibitor of SGLT2 has been shown to support blood sugar regulation. It also contributes reduction in HbA1c and body weight. It also lowers the risk of cardiovascular mortality and heart failure.
Van Baar et al	Narrative Review	2018	Combining SGLT2 inhibitors with GLP-1 receptor may provide enhanced benefits in managing blood glucose, promoting weight loss, lowering blood pressure, and kidney protection.
Santos et al	Systematic Review	2017	SGLT-2 inhibitors reduce blood glucose by inducing glycosuria in an insulin- independent manner. They also improve glycemic control, reduce weight and BP, and show cardiovascular and renal benefits.
Chun & Butts	Narrative Review	2020	SGLT-2 and dual SGLT-1/2 inhibitors show efficacy in lowering A1C and promoting weight loss with low hypoglycemia risk, especially when used without insulin or sulfonylureas. These agents also show cardiovascular safety benefits.
Milder et al	Meta-analysis	2022	Starting treatment with a combination of SGLT2 inhibitor and metformin has shown better blood glucose regulation and weight loss. However, this approach may slightly raise the risk of genital infection and diarrhea.
Yoshifumi Saisho	Narrative Review	2020	SGLT2 inhibitors such as empagliflozin, canagliflozin, and dapagliflozin are used either alone or in combination with agents like metformin, insulin, or GLP-1 receptor agonists for the treatment of type 2 diabetes, heart failure, and chronic kidney disease.
Rahul P. Kshirsagar	Comprehensive Review	2020	These drugs reduce glycemic status by blocking glucose reabsorption in the kidneys, which results in greater excretion of sugar through the urine. They can be prescribed on their own or alongside other antidiabetic agents.
Bo Xu, Shaoqian Li	Narrative Review	2022	These agents reduce hyperglycemia by inhibiting renal glucose reabsorption, and also provide cardiovascular and renal protective effects. They are approved for use in T2DM, heart failure (HFrEF and HFpEF), and chronic kidney disease, with demonstrated benefits in clinical trials and meta-analyses.
Alvaro Garcia- Ropero	**Narrative Review**	**2018**	**SGLT2 inhibitors contribute to improved glycemic regulation and increase weight loss. It also provides cardiovascular and renal advantages, thereby transforming the therapeutic approach to manage T2DM.**

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Table 3: Comparison of GLP-1 Receptor Agonists and SGLT2 Inhibitors

Aspect	GLP-1 Receptor Agonists	SGLT2 Inhibitors	Author(s) & Year
Core Pathophysiological Target	Poor insulin release, high glucagon, weak incretin response	Kidneys reabsorb too much glucose, worsening high blood sugar	Jaggy S (2023); Davidson (2019)
Mechanism of action	Help pancreas release insulin, lower glucagon, slow down digestion	Block sugar reabsorption in kidneys, increase sugar loss in urine	(Brunton & Wysham, 2020) (Mashima et al., 2020)
Therapeutic Use in T2DM	Improve blood sugar levels, help with weight loss, protect the heart	Lower blood sugar, reduce weight, protect the heart and kidneys	(Joshi et al., 2024) (Fioretto et al., 2016)
Effect on Body Weight	Reduce appetite, support weight loss	Cause calorie loss, support weight reduction	(Cornell, 2020) (Simes & Mac Gregor, 2019)
Cardiovascular Benefits	Lower risk of heart attacks and strokes in T2DM patients	Lower risk of heart failure and related hospitalizations	(Verma & McMurray, 2018)
Kidney Benefits	Some protection against kidney damage	Strong kidney protection, especially in patients with kidney problems	(Baars et al., 2024) (Fioretto et al., 2016)
Risk of hyperglycemia	Very low when not used with insulin or sulfonylureas	Very low due to insulin-independent action	(Joshi et al., 2024) (Xu et al., 2020)
Common Side Effects	Nausea, vomiting, stomach upset	Genital infections, dehydration, rare ketoacidosis	(Joshi et al., 2024) (Santos et al., 2017)

DISCUSSION

The findings of this review reinforce the multifactorial nature of Type 2 Diabetes Mellitus (T2DM), emphasizing that its pathogenesis is rooted in a complex interplay between insulin resistance and progressive β-cell dysfunction. Insulin resistance, resulting from impaired intracellular signaling mechanisms such as defects in IRS-1/2 and PI3-kinase pathways, limits glucose uptake in peripheral tissues even among non-obese individuals. Although weight loss may offer partial metabolic recovery, these signaling abnormalities often persist, indicating intrinsic cellular defects that contribute to disease chronicity (12,13). As insulin demand increases, β-cell performance deteriorates due to lipotoxicity and glucotoxicity, further compounded by mitochondrial dysfunction, ATP depletion, and impaired insulin granule trafficking. This mitochondrial impairment, particularly evident in diminished glucose-stimulated insulin secretion, represents a key mechanistic deficit in the diabetic state (14,15). The twin-cycle hypothesis provides a compelling model for the interdependence between hepatic fat accumulation and pancreatic lipotoxicity, both of which aggravate insulin resistance and compromise insulin secretion. Excess hepatic triglyceride synthesis exacerbates pancreatic steatosis, initiating a self-reinforcing metabolic loop. Additionally, the overexpression of lipogenic genes driven by hyperinsulinemia worsens metabolic overload and inflammation. These interrelated pathophysiological disturbances are consistent with earlier models of metabolic inflexibility and chronic subclinical inflammation in T2DM (16,17).

The therapeutic findings related to GLP-1 receptor agonists align with existing literature demonstrating their pleiotropic benefits. Agents such as dulaglutide, liraglutide, and semaglutide not only improve glycemic control but also contribute to significant weight reduction, largely through appetite suppression and delayed gastric emptying. Clinical outcomes further suggest that dulaglutide offers substantial HbA1c reduction, while liraglutide may be more effective in lowering body mass index, highlighting the nuanced advantages of agent-specific interventions (18-21). Oral semaglutide extends these benefits to patients reluctant to use injectable formulations, thereby improving treatment accessibility and adherence. The safety profile of GLP-1RAs remains favorable, with most gastrointestinal side effects being transient and mild. Notably, dual agonists such as tirzepatide have emerged as a major therapeutic advancement,

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outperforming high-dose semaglutide in glycemic control and weight loss while maintaining a similar adverse event profile. These agents also demonstrate cardiovascular and renal protective properties, consistent with anti-inflammatory and antioxidative effects observed in long-term outcome studies (22,23). SGLT2 inhibitors offer a complementary mechanism of action by promoting urinary glucose excretion, which leads to reductions in blood glucose levels, systolic blood pressure, and body weight. The evidence supports their role in reducing heart failure hospitalization and slowing the progression of chronic kidney disease, extending their utility well beyond glycemic control. Mechanistic hypotheses involving improved myocardial energetics, reduced preload and afterload, and attenuation of renal hyperfiltration have been supported by both clinical and preclinical data. An additional area of growing interest is the potential for SGLT2 inhibitors to modulate gut microbiota, which may in turn enhance endogenous GLP-1 secretion via tryptophan-derived metabolites, although human data remain inconclusive due to high inter-individual variability in microbiota composition (24).

Combination therapy involving GLP-1RAs and SGLT2 inhibitors has demonstrated incremental benefits in HbA1c and weight reduction, particularly in overweight patients or those with cardiovascular comorbidities. This synergistic approach not only avoids hypoglycemia but also addresses multiple pathophysiological targets concurrently. The additive effect observed in large pooled analyses underscores the value of individualized, multimodal treatment strategies in T2DM management. Despite the strengths of this review—including a broad search strategy, inclusion of diverse study designs, and a focus on real-world clinical relevance—several limitations must be acknowledged. The heterogeneity in study populations, treatment durations, and outcome measures limited the feasibility of meta-analysis and may have introduced variability in effect estimates. Furthermore, the reliance on narrative synthesis in the absence of standardized bias scoring tools restricts the ability to quantify the overall evidence quality. Some included studies, particularly narrative reviews, lacked uniform reporting standards, which may affect interpretability. Additionally, emerging therapies such as tirzepatide and oral semaglutide require longer-term safety data to confirm their durability and broader applicability across diverse populations. Future research should prioritize large-scale, head-to-head comparative trials with diverse populations to better understand differential responses among ethnicities, age groups, and comorbidity profiles. Mechanistic studies exploring the interplay between gut microbiota, incretin biology, and mitochondrial function may also yield novel insights. Furthermore, evaluating the long-term cardiovascular and renal outcomes of newer agents in real-world settings will be essential for refining treatment algorithms. In summary, this discussion affirms that both GLP-1 receptor agonists and SGLT2 inhibitors represent cornerstone therapies in modern T2DM management. Their ability to modulate not only glucose metabolism but also weight, cardiovascular risk, and renal decline underscores their multidimensional utility. However, optimizing their clinical application requires an individualized approach that integrates patient-specific factors with evolving evidence.

CONCLUSION

This systematic review highlights the multifactorial nature of Type 2 Diabetes Mellitus and emphasizes the growing relevance of GLP-1 receptor agonists and SGLT2 inhibitors in addressing its complex pathophysiology. Unlike traditional therapies that primarily target glycemic control, these agents offer broader metabolic, cardiovascular, and renal benefits while also improving insulin sensitivity and β-cell function. Their complementary mechanisms mark a pivotal shift toward more individualized and organ-protective treatment strategies. Despite some tolerability concerns, their overall therapeutic profile supports their integration into routine care for patients with T2DM, particularly those with high cardiometabolic risk. The findings reinforce the need for continued research to optimize personalized interventions and advance long-term disease management.

AUTHOR CONTRIBUTION

Author	Contribution
Muhammad Uzair	Substantial Contribution to study design, analysis, acquisition of Data Manuscript Writing Has given Final Approval of the version to be published
Nabiha Khursheed	Substantial Contribution to study design, acquisition and interpretation of Data Critical Review and Manuscript Writing Has given Final Approval of the version to be published
Abeera Nasir	Substantial Contribution to acquisition and interpretation of Data Has given Final Approval of the version to be published
Muskan Saleem	Contributed to Data Collection and Analysis

Author	Contribution
	Has given Final Approval of the version to be published
Abdul Ahad	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Zainab Ali	Substantial Contribution to study design and Data Analysis Has given Final Approval of the version to be published
Aiman Noreen	Contributed to study concept and Data collection Has given Final Approval of the version to be published
Muhammad Sulaiman Saeed*	Writing - Review & Editing, Assistance with Data Curation

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