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Review Article

COMPARATIVE EFFICACY AND SAFETY OF SGLT-2 AND DPP-4 INHIBITORS AS ADD-ON THERAPIES IN PATIENTS WITH TYPE 2 DIABETES MELLITUS: A SYSTEMATIC REVIEW

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Abstract

Background: The relentless orchestration and uncompromising regulation of Type 2 Diabetes Mellitus (T2DM) frequently demand an intensified combinatorial pharmacotherapeutic strategy to enforce stringent glycemic homeostasis. Sodium-glucose Co-Transporter 2 (SGLT2) Inhibitors and Dipeptidyl Peptidase-4 (DPP4) Inhibitors emerge as indispensable reinforcements for patients exhibiting persistent glycemic dysregulation despite exhaustive Metformin monotherapy.

Objective: This exhaustive analytical review meticulously scrutinizes the comparative therapeutic efficacy and multidimensional safety profile of Sodium-Glucose Co-Transporter 2 (SGLT2) inhibitors versus Dipeptidyl Peptidase-4 (DPP4) inhibitors when deployed as adjunctive pharmacotherapeutic interventions in the intricate management paradigm of Type 2 Diabetes Mellitus (T2DM).

Methods: A rigorous and methodologically structured literature exploration was undertaken, encompassing randomized controlled trials (RCTs) and high-quality observational studies that delineate the comparative efficacy and safety profiles of Sodium-Glucose Co-Transporter 2 (SGLT2) inhibitors and Dipeptidyl Peptidase-4 (DPP4) inhibitors within this therapeutic framework.

Efficacy Outcomes: The assessment of therapeutic efficacy was predominantly quantified through variations in glycated hemoglobin (HbA1c) levels, fasting plasma glucose (FPG), and body weight. Evidence consistently demonstrates that Sodium-Glucose Co-Transporter 2 (SGLT2) inhibitors elicit superior reductions in HbA1c and body weight relative to Dipeptidyl Peptidase-4 (DPP4) inhibitors. Furthermore, SGLT2 inhibitors confer additional cardiometabolic advantages, including significant reductions in blood pressure and amelioration of key cardiovascular risk parameters.

Safety Outcomes: The pharmacovigilance assessment encompassed an extensive evaluation of adverse event profiles, including hypoglycemic episodes, urinary tract infections (UTIs), genital infections, and

cardiovascular ramifications. Sodium-Glucose Co-Transporter 2 (SGLT2) inhibitors demonstrated a disproportionately elevated predisposition to UTIs and genital infections, attributed to their glucosuric mechanism, whereas Dipeptidyl Peptidase-4 (DPP4) inhibitors exhibited a comparatively superior safety paradigm, marked by a diminished incidence of UTIs and an absence of statistically significant augmentation in hypoglycemic episodes.

Conclusion: SGLT2 inhibitors manifest an advanced glycemic regulatory capacity, coupled with auxiliary metabolic enhancements, particularly in weight reduction and cardiovascular risk attenuation. However, their therapeutic utility is counterbalanced by an escalated vulnerability to genitourinary infections. In contrast, DPP4 inhibitors emerge as a pharmacologically safer alternative, albeit demonstrating a comparatively attenuated efficacy profile. The dichotomous selection between these pharmacotherapeutic agents necessitates a meticulously stratified, patient-centric approach, rigorously integrating individualized clinical parameters such as intrinsic cardiovascular risk burden, infection susceptibility, and drug tolerability thresholds.

Keywords: Type 2 Diabetes Mellitus, SGLT2 Inhibitors, DPP4 Inhibitors, Glycemic Control, Add-on Therapy

1. Introduction

Type 2 Diabetes Mellitus (T2DM) has escalated into a pervasive global health crisis, afflicting millions across diverse populations and serving as a formidable catalyst for morbidity and mortality through its multifaceted and debilitating complications. Effective management of T2DM involves a combination of lifestyle modifications and pharmacotherapy aimed at achieving and maintaining optimal glycemic control to prevent complications. Metformin is generally the first-line pharmacologic treatment, but many patients eventually require additional therapies to achieve target glycemic levels. Among the various add-on therapies, sodium-glucose co-transporter 2 (SGLT2) inhibitors and dipeptidyl peptidase-4 (DPP4) inhibitors have gained prominence due to their efficacy and safety profiles.

2. Research Questions

1. What molecular mechanisms drive the superior glycemic control of SGLT2 inhibitors over DPP4 inhibitors?
2. How do the divergent cardio metabolic effects of SGLT2 and DPP4 inhibitors influence long-term mortality in T2DM?
3. What are the pathophysiological determinants of increased infection risk with SGLT2 inhibitors compared to DPP4 inhibitors?
4. How do SGLT2 and DPP4 inhibitors differentially modulate renal hemodynamics in diabetic nephropathy?
5. Which patient factors help decide whether SGLT2 or DPP4 inhibitors work better in Type 2 Diabetes?

3. Methods

3.1 Search Strategy

A systematic review of the literature was conducted, focusing on randomized controlled trials (RCTs) and observational studies comparing the efficacy and safety of SGLT2 inhibitors and DPP4 inhibitors as add-on therapy in T2DM patients. Primary efficacy outcomes included changes in glycated hemoglobin (HbA1c), fasting plasma glucose (FPG), and body weight. Safety outcomes were assessed based on reported adverse events, such as hypoglycemia, urinary tract infections (UTIs), genital infections, and cardiovascular events. Relevant databases, including PubMed, Embase, and Cochrane Library, were searched up to December 2024. Studies were selected based on predefined inclusion criteria, and data were extracted and analyzed qualitatively.

3.2 Inclusion Criteria

A. Study Design: Randomized controlled trials (RCTs), well-designed observational studies, meta-analyses, and systematic reviews.

B. Population: Adults (≥18 years) diagnosed with Type 2 Diabetes Mellitus (T2DM).

C. Intervention: Administration of sodium-glucose co-transporter 2 (SGLT2) inhibitors (e.g., empagliflozin, canagliflozin, dapagliflozin) and/or dipeptidyl peptidase-4 (DPP4) inhibitors (e.g., sitagliptin, linagliptin, saxagliptin) as adjunctive therapy to standard diabetes treatment.

D. Comparison: Direct comparative studies between SGLT2 inhibitors and DPP4 inhibitors or placebo-controlled trials with subgroup analyses relevant to these drug classes.

E. Outcome Measures: Assessment of key therapeutic outcomes, including changes in glycated hemoglobin (HbA1c), fasting plasma glucose (FPG), body weight, body mass index (BMI), cardiovascular risk markers, adverse event profiles, renal function, and treatment adherence.

F. Study Duration: Minimum follow-up period of 12 weeks to ensure meaningful clinical outcomes.

G. Language: Only studies published in English.

H. Publication Date: Research published within the last decade to maintain contemporary relevance.

3.3 Exclusion Criteria

A. Publication Date: Case reports, editorials, conference abstracts, review articles without systematic methodology, and non-peer-reviewed publications.

B. Population: Studies involving patients with Type 1 Diabetes Mellitus, gestational diabetes, or prediabetes.

C. Intervention: Research including antidiabetic drug classes other than SGLT2 or DPP4 inhibitors without explicit subgroup analyses for these medications.

D. Outcome Measures: Studies limited to in vitro experiments, animal models, or pharmacokinetic evaluations without clinical relevance.

E. Study Duration: Trials with follow-up periods shorter than 12 weeks.

E. Language: Non-English studies that lack accessible full-text translations.

4. Discussion

4.1 Efficacy Comparison

Glycated Hemoglobin (HbA1c) Reduction

HbA1c is a critical marker for long-term glycemic control, reflecting average blood glucose levels over the preceding two to three months. Both sodium-glucose co-transporter 2 antagonists and dipeptidyl peptidase-4 modulators exhibit significant efficacy in attenuating HbA1c levels when integrated with metformin therapy; however, the former generally induces a more substantial glycemic decline. A meta-analysis of 20 RCTs involving over 10,000 patients found that SGLT2 inhibitors reduced HbA1c by an average of 0.6-0.8% from baseline, while DPP4 inhibitors reduced HbA1c by 0.5-0.7%[1,2]. For instance, a 52-week study comparing canagliflozin and sitagliptin reported mean HbA1c reductions of 0.9% and 0.7%, respectively[3]. Similarly, empagliflozin demonstrated superior HbA1c reduction compared to linagliptin in several head-to-head trials[4].

Fasting Plasma Glucose (FPG)

Fasting plasma glucose serves as a critical biomarker for assessing glycemic regulation. SGLT2 inhibitors significantly reduce FPG levels due to their mechanism of increasing renal glucose excretion. DPP4 inhibitors primarily exert their glucose-lowering effects postprandially. Studies indicate that SGLT2 inhibitors reduce FPG by approximately 1.5-2.0 mmol/L, whereas DPP4 inhibitors result in reductions of around 0.8-1.2 mmol/L[5]. A clinical trial evaluating dapagliflozin and saxagliptin demonstrated a reduction in fasting plasma glucose levels by 1.9 mmol/L with dapagliflozin, compared to a 1.1 mmol/L decrease with saxagliptin over a 24-week treatment period[6].

Body Weight

Weight management is crucial in T2DM care, as excess body weight exacerbates insulin resistance. SGLT2 inhibitors, due to their glucosuric effect, are linked to substantial reductions in body weight. On the other hand, DPP4 inhibitors generally maintain a stable weight profile without significant changes. Extensive clinical investigations have consistently affirmed that SGLT2 inhibitors contribute to an average weight reduction ranging from 2 to 3 kg[7]. For instance, a 26-week clinical trial demonstrated that individuals receiving empagliflozin exhibited an average weight reduction of 2.5 kg, whereas those treated with sitagliptin showed minimal to no significant weight change[8]. This weight loss is partially attributed to the calorie loss associated with urinary glucose excretion[9].

4.2 Safety Comparison

Hypoglycemia

Hypoglycemia is a common concern in diabetes management. SGLT2 inhibitors and DPP4 inhibitors demonstrate an inherently low propensity for hypoglycemia, primarily due to their mechanistic reliance on endogenous glucose concentrations to modulate glycemic reductions. In a pooled analysis of RCTs, the incidence of hypoglycemia was low for both drug classes, with rates of less than 5%[10]. However, the potential for hypoglycemia escalates when SGLT2 and DPP4 inhibitors are used alongside insulin secretagogues such as sulfonylureas or exogenous insulin, which independently drive glucose lowering irrespective of physiological needs[11].

Urinary Tract Infections and Genital Infections

SGLT2 inhibitors predispose patients to a higher incidence of urinary tract infections and genital mycotic infections due to enhanced glycosuria, which creates a favorable environment for microbial proliferation. Meta-analyses have demonstrated a significantly elevated incidence of urinary tract and genital infections among patients using SGLT2 inhibitors compared to placebo and other antidiabetic agents[12]. For instance, urinary tract infections occur in approximately 8–10% of patients treated with SGLT2 inhibitors, whereas the prevalence is lower, around 4–6%, in those receiving DPP4 inhibitors[13]. Genital infections are documented in approximately 5–10% of patients receiving SGLT2 inhibitors, a markedly higher incidence compared to the 1–2% reported in those treated with DPP4 inhibitors[14].

Cardiovascular Outcomes

Cardiovascular disease is a leading cause of mortality in patients with Type 2 Diabetes Mellitus. Recent cardiovascular outcome trials (CVOTs) have provided valuable insights into the cardiovascular effects of SGLT2 and DPP4 inhibitors. SGLT2 inhibitors have demonstrated robust cardiovascular benefits. The EMPA-REG OUTCOME trial showed that empagliflozin significantly reduced the risk of major adverse cardiovascular events (MACE) by 14%, cardiovascular death by 38%, and heart failure hospitalization by 35%[15]. Similarly, the CANVAS program reported that canagliflozin reduced MACE by 14%[16]. In contrast, CVOTs for DPP4 inhibitors have not shown significant cardiovascular benefits. For example, the TECOS trial found that sitagliptin neither increased nor decreased the risk of MACE compared to placebo[17]. The SAVOR-TIMI 53 trial with saxagliptin and the EXAMINE trial with alogliptin also reported neutral cardiovascular outcomes[18,19].

4.3 Mechanisms of Action

SGLT2 Inhibitors

SGLT2 inhibitors function by selectively inhibiting the SGLT2 transporter within the proximal renal tubules, thereby disrupting the reabsorption of approximately 90% of filtered glucose and promoting its excretion through urine[20]. This insulin-independent mechanism enables SGLT2 inhibitors to remain effective even in individuals with advanced beta-cell dysfunction[21]. The glucosuric effect of SGLT2 inhibitors also leads to mild osmotic diuresis, which can contribute to reductions in

blood pressure and weight loss[22]. Moreover, these pharmacological agents have demonstrated advantageous effects on renal outcomes, likely due to reductions in intraglomerular pressure and improvements in glycemic contro[23].

DPP4 Inhibitors

DPP4 inhibitors enhance the incretin system, which plays a crucial role in glucose homeostasis. They work by inhibiting the enzyme dipeptidyl peptidase-4 (DPP4), which degrades incretin hormones such as GLP-1 and GIP[24]. These hormones stimulate insulin secretion in a glucose-dependent manner and suppress glucagon release, thereby improving postprandial glucose control[25]. Because DPP4 inhibitors do not directly increase insulin levels, their risk of causing hypoglycemia is low. They also do not typically affect body weight, making them a weight-neutral option for patients[26]. However, their efficacy in reducing HbA1c is generally less pronounced than that of SGLT2 inhibitors[27].

Patient Populations and Individualized Treatment

The selection between SGLT2 inhibitors and DPP4 inhibitors should be tailored to individual patient characteristics and comorbidities.

Cardiovascular Risk

For patients with established cardiovascular disease or high cardiovascular risk, SGLT2 inhibitors are generally preferred due to their demonstrated cardiovascular benefits[28]. These agents substantially lower the risk of cardiovascular events and mortality, establishing them as a crucial therapeutic choice for such patients[29].

Renal Function

Patients with chronic kidney disease (CKD) derive substantial benefits from SGLT2 inhibitors, which have demonstrated a capacity to enhance renal outcomes and decelerate CKD progression[30]. Nevertheless, their clinical utility is constrained in individuals with advanced renal impairment (eGFR < 30 mL/min/1.73 m^2), as their therapeutic efficacy markedly declines in parallel with deteriorating kidney function[31]. DPP4 inhibitors can be used across a broader range of renal functions, making them suitable for patients with mild to moderate renal impairment[32]. Dose adjustments are often necessary based on the level of renal function[33].

Risk of Infections

For patients prone to recurrent UTIs or genital infections, SGLT2 inhibitors require cautious use. DPP4 inhibitors may be preferred due to the lower risk of these adverse events compared to SGLT2 inhibitors[34]. This consideration is particularly important in patients already prone to infections or those with conditions predisposing them to infections[35].

Weight Management

Patients who are overweight or obese and seeking weight loss benefits may find SGLT2 inhibitors advantageous due to their ability to induce weight loss[36]. Conversely, DPP4 inhibitors may be more appropriate for patients who are already maintaining a healthy weight. or those for whom weight loss is not a primary treatment goal[37].

Long-Term Outcomes and Ongoing Research

Long-term outcomes and ongoing research continue to shape the understanding and utilization of both drugs.

Cardiovascular Outcomes

The cardiovascular benefits of SGLT-2 have been well-documented in large-scale CVOTs[38]. Ongoing research is exploring the mechanisms behind these benefits, including potential anti-inflammatory and anti-atherosclerotic effects[39]. Further studies are also assessing the impact of these agents on heart failure outcomes and other cardiovascular parameters[40].

Renal Outcomes

SGLT-2 inhibitors have gained considerable attention, with studies such as the CREDENCE trial highlighting significant benefits in patients with CKD[41]. These findings are prompting further investigation into the potential of SGLT2 inhibitors

to delay the progression of kidney disease in broader populations[42].

Safety and Tolerability

While the safety profiles of both SGLT2 and DPP-4 inhibitors are generally well-tolerated ongoing pharmacovigilance and long-term studies are essential to monitor for rare adverse events and ensure comprehensive safety data[43]. The risk of diabetic ketoacidosis (DKA) with SGLT2 inhibitors, though low, remains an active area of research to identify predisposing factors and develop mitigation strategies[44].

Cost-Effectiveness and Accessibility

The cost-effectiveness and accessibility of SGLT2 and DPP4 inhibitors are important considerations for healthcare systems and patients.

Cost-Effectiveness

SGLT2 inhibitors are cost-effective in certain populations, particularly those with high cardiovascular risk due to their dual benefits on glycemic control and cardiovascular outcomes[45]. However, the higher acquisition costs of these agents compared to older diabetes medications can be a barrier[46]. DPP4 inhibitors, while generally less expensive than SGLT2 inhibitors, still represent a higher cost compared to generic options like metformin and sulfonylureas[47]. Cost-effectiveness analyses often consider factors such as long-term health outcomes, reduction in complication rates, and overall healthcare utilization[48].

Accessibility

The accessibility of these medications varies globally, influenced by factors such as healthcare infrastructure, insurance coverage, and national formulary listings[49]. Efforts to improve accessibility include the availability of generic versions, inclusion in essential medicines lists, and policy initiatives to subsidize costs for patients[50].

Patient and Provider Perspectives

Patient and provider perspectives play a critical role in the successful implementation of T2DM treatment regimens.

Patient Preferences

Patient preferences for medication attributes, including efficacy, side effects, convenience, and impact on quality of life are crucial for adherence and long-term success[51]. Studies indicate that patients prioritize factors such as hypoglycemia risk, weight effects, and cardiovascular benefits when selecting between SGLT2 and DPP4 inhibitors[52].

Provider Recommendations

Healthcare providers must balance clinical guidelines, individual patient characteristics, and preferences when recommending treatment options[53]. Continuing medical education and access to updated evidence-based guidelines are essential for providers to make informed decisions[54].

Future Directions

The management of T2DM is constantly advancing, driven by ongoing research and development focused on enhancing patient outcomes.

Emerging Therapies

Newer therapies and combination treatments are under investigation, offering the potential for enhanced efficacy and safety profiles[55]. For instance, dual inhibitors targeting both SGLT2 and SGLT1, or combined GLP-1 receptor agonists and DPP4 inhibitors, are being explored[56].

Personalized Medicine

Advancements in personalized medicine, including genetic profiling and biomarker identification, may enable more tailored approaches to T2DM treatment[57]. Personalized strategies could optimize therapeutic outcomes by aligning treatment choices with individual patient characteristics and responses[58].

5. Conclusion

To conclude, both SGLT2 and DPP4 inhibitors are valuable add-on therapies for patients with T2DM

who experience inadequate glycemic control with metformin. SGLT2 inhibitors offer superior glucose-lowering effects, promote weight loss, and confer cardiovascular benefits but are associated with an increased risk of infections. Conversely, DPP4 inhibitors provide a well-tolerated safety profile with moderate efficacy. The selection between these therapeutic options should be tailored to individual patient profiles, considering factors such as cardiovascular risk, infection susceptibility, and overall treatment goals. Ongoing long-term research is essential to further validate these findings and optimize clinical decision-making in the management of T2DM.

6. Conflict of Interest: None

7. References

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