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EFFICACY AND SAFETY PROFILE OF DPP-4 INHIBITORS AS ADD-ON THERAPY IN PATIENTS WITH TYPE 2 DIABETES: A COMPREHENSIVE REVIEW

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ABSTRACT: Aim: This study aimed to evaluate the efficacy and safety profile of DPP-4 inhibitors as add-on therapy in patients with type 2 diabetes. The study is important because DPP-4 inhibitors have been widely prescribed, and understanding their comprehensive effects is essential for better patient outcomes. **Methods:** An extensive literature search has been conducted using multiple databases, such as PubMed, Cochrane Library, Scopus, Web of Science, and Google Scholar. All results have been analyzed based on inclusion and exclusion criteria, and their findings are displayed statistically to ensure accurate comparisons between treatment groups. **Results:** DPP-4 inhibitors demonstrate significant efficacy in managing type 2 diabetes mellitus (T2DM), leading to a reduction in glycated hemoglobin (HbA1c) levels by 0.9% (9 mmol/mol; $p < 0.0001$) and fasting blood glucose (FBG) by 1.15 mmol/L (19.82 mg/dL; $p = 0.001$) among a cohort of 105 individuals. Notably, sitagliptin exhibited a remarkable HbA1c reduction of 1.66% (19 mmol/mol; $p < 0.0001$). These inhibitors also significantly curtailed glycemic variability, as evidenced by a mean amplitude of glycemic excursions (MAGE) reduction of -14.61 (95% CI = -19.00 to -10.21; $p < 0.0001$). Although linagliptin showed a non-significant weight increase of 0.2 ± 0.2 kg ($P = 0.349$), the overall cardiovascular benefits of DPP-4 inhibitors are noteworthy, with a 31% reduction in the risk of cardiovascular mortality or heart failure rehospitalization (HR: 0.69; $P = 0.002$). The renal protective effects include alleviation of albuminuria and slowing of chronic kidney disease progression. Common adverse reactions include nasopharyngitis and gastrointestinal disturbances, while serious adverse effects, such as pancreatitis and severe dermatological reactions, warrant close monitoring and caution.

INTRODUCTION: Diabetes mellitus is a multifaceted metabolic disorder marked by dysregulation in protein, lipid, and carbohydrate metabolism, alongside chronic hyperglycemia.

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This persistent elevation of blood glucose is attributed to inadequate insulin secretion or impaired insulin function.

The condition precipitates progressive, systemic damage, functional deterioration, and eventual failure of critical organs, including the heart, vasculature, kidneys, retinas, and nervous system [1]. Diabetes is stratified into distinct classifications, notably type 1, type 2, and gestational diabetes, with type 2 emerging as the predominant variant. Type 1 diabetes mellitus (T1DM) constitutes an

estimated 5% to 10% of occurrences. In contrast, type 2 diabetes mellitus (T2DM) accounts for a staggering 90% to 95% of the diagnosed population [2]. In 2019, the global burden of diabetes mellitus (DM) stood at 4.63 million cases. Forecasts indicate a sharp escalation, with prevalence projected to surge to 10.2% (578 million) by 2030 and 10.9% (700 million) by 2045, signaling a significant global health challenge in the coming decades [3]. India currently has 62.4 million individuals living with diabetes, a figure projected to surpass 100 million by 2030. The prevalence of diabetes among adults in India has escalated significantly, reaching approximately 20% in urban areas and around 10% in rural regions [4].

It is estimated that 15% of individuals with diabetes will develop coronary artery disease, 22% will suffer from retinopathy, potentially leading to blindness, 38% will experience chronic kidney disease, and 3% will encounter vascular complications that could result in amputation. These statistics underscore the critical need for effective disease management to avert such complications, emphasizing the necessity for innovative therapies and advanced pharmacological interventions [5]. Aside from adopting healthier dietary habits and maintaining physical activity, several approved therapeutic options are available. These encompass various forms of insulin short-acting, intermediate-acting, and long-acting as well as oral agents such as metformin (a biguanide), thiazolidinediones, sulfonylureas, and meglitinides [6]. Pharmacological agents like sulfonylureas (SUs) are associated with considerable risks. These include the potential for hypoglycemia (reduced blood glucose levels), weight gain, a heightened incidence of cardiovascular complications, and an increased mortality risk [7].

Mechanism of Action: Dipeptidyl peptidase-4 (DPP-4) inhibitors are sophisticated oral hypoglycemic agents that potentiate postprandial insulinotropic responses. These agents operate through selective inhibition of the DPP-4 enzyme, which is intrinsically responsible for the rapid proteolytic degradation of incretin hormones such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). By inhibiting DPP-4, these compounds prolong the bioavailability and bioactivity of incretins, thereby augmenting glucose-dependent insulin secretion from pancreatic β-cells and concurrently attenuating glucagon release from α-cells. This biochemical modulation decreases hyperglycemic excursions while minimizing the risk of hypoglycemia, a common concern with alternative antidiabetic therapies. Furthermore, DPP-4 inhibitors exert a cytoprotective effect on β-cells and are hypothesized to exhibit anti-inflammatory properties, underscoring their multifunctional role in type 2 diabetes mellitus management. Representative agents within this pharmacological class include sitagliptin, saxagliptin, and linagliptin [8].

Research Questions:

1. How do DPP-4 inhibitors impact glycaemic control, including HbA1c, FBS, and PPBS, when used as an add-on to existing therapy?
2. What is the impact of DPP-4 inhibitors on body weight over time?
3. Are there any significant differences in the lipid profile (total cholesterol, HDL, LDL, triglycerides) before and after DPP-4 inhibitor therapy?
4. What are the most common adverse drug reactions associated with DPP-4 inhibitors?
5. How do DPP-4 inhibitors compare to other classes of anti-diabetic medications in terms of efficacy and safety?

METHODS:

Search Strategy: A comprehensive literature search was conducted using multiple electronic databases, including PubMed, Cochrane Library, and Google Scholar. The search terms included “DPP-4 inhibitors,” “type 2 diabetes,” “efficacy,” “safety profile,” and “add-on therapy.” Articles published from 2019 to 2024 were included.

Evaluation of Efficacy and Safety: The evaluation of efficacy and safety in this review focused on several key outcome measures:

Primary Efficacy Outcome: The primary efficacy measure was the glycated hemoglobin (HbA1c) change from baseline levels. This is a critical

indicator of long-term glycemic control in patients with type 2 diabetes.

Secondary Efficacy Outcomes:

- The proportion of patients achieving an HbA1c level of <7.0% (53 mmol/mol), reflects effective diabetes management.
- Mean changes in fasting plasma glucose (FPG) and postprandial glucose (PPG) levels, providing insight into daily glycemic control.
- Changes in body weight, as weight management, is a vital aspect of diabetes care.

Safety and Tolerability Indicators: The safety profile was assessed by monitoring the occurrence of adverse events, including:

1. Hypoglycemia episodes can lead to significant health risks.
2. Gastrointestinal issues (e.g., nausea, diarrhea) are often associated with DPP-4 inhibitors.
3. Cardiovascular safety outcomes to evaluate any cardiovascular events linked to treatment.
4. Incidents of renal function impairment or acute pancreatitis, as these conditions may arise from treatment.
5. The occurrence of upper respiratory tract infections and headaches are common adverse events related to DPP-4 inhibitors.

Inclusion Criteria:

1. Patients aged 18 to 75 were selected.
2. Patients with type 2 diabetes.
3. Patients using DPP-4 inhibitors as add-on therapy.
4. Patients with HbA1c greater than 6.5%.
5. Patients who gave consent for the study.

Exclusion Criteria:

1. Patients with type 1 diabetes.
2. Patients with end-stage renal disease.
3. Pregnant and lactating women.

Efficacy: DPP-4 inhibitors have demonstrated efficacy in multiple clinical trials and meta-analyses. When taken as an add-on therapy to metformin, these studies typically show significant improvements in glycemic control (HbA1c), neutral effects on body weight, and a low risk of hypoglycemia.

In a retrospective cross-sectional analysis encompassing a cohort of 105 individuals diagnosed with type 2 diabetes mellitus (T2DM), the integration of DPP-4 inhibitors (DPP-4i) as adjunctive therapeutic agents manifested a statistically significant diminution in glycated hemoglobin (HbA1c) by 0.9% (equivalent to 9 mmol/mol; $p < 0.0001$) and a concomitant reduction in fasting blood glucose (FBG) levels by 1.15 mmol/L (19.82 mg/dL; $p = 0.001$), while exhibiting no discernible alterations in body mass ($p = 0.745$). Notably, Sitagliptin emerged as the most efficacious agent, achieving a remarkable reduction in HbA1c of 1.66% (19 mmol/mol; $p < 0.0001$).[9]Subsequently, a systematic review and meta-analysis of randomized controlled trials (RCTs) meticulously evaluated the efficacy of DPP-IV inhibitors in attenuating glycemic variability (GV), as measured by the mean amplitude of glycemic excursions (MAGE).

This comprehensive meta-analysis incorporated seven RCTs and delineated that DPP-IV inhibitors significantly abated MAGE when juxtaposed with alternative oral antihyperglycemic pharma-cotherapies, yielding a mean difference of −14.61 (95% CI = −19.00 to −10.21; $p < 0.0001$). Furthermore, there was an absence of substantial heterogeneity among sulfonylureas, as evidenced by a mean difference of −14.93 ($p < 0.0001$). Intriguingly, initial combination therapy utilizing DPP-IV inhibitors demonstrated markedly superior efficacy in curtailing MAGE compared to incremental add-on therapies ($p = 0.006$).

Collectively, these findings posit that DPP-IV inhibitors constitute a formidable therapeutic strategy for the modulation of glycemic variability in patients afflicted with type 2 diabetes, thereby underscoring the imperative for further investigative pursuits to validate and elucidate these compelling observations [10]. DPP-4 inhibitors are a highly effective class of medications for

managing type 2 diabetes mellitus (T2DM), demonstrating significant reductions in HbA1c and fasting blood glucose without adversely affecting body weight. Their efficacy in decreasing glycemic variability is particularly noteworthy, as it is crucial for preventing complications associated with T2DM. The enhanced outcomes from initial combination therapy further underscore their potential in personalized treatment strategies. While the findings are compelling, further research with larger cohorts and longer follow-ups is essential to confirm their long-term benefits and safety. Overall, DPP-4 inhibitors should be considered a valuable addition to diabetes management protocols.

Body Weight: In a 24-week, randomized, open-label study assessing the comparative efficacy of empagliflozin versus linagliptin as adjuncts to premixed insulin for uncontrolled type 2 diabetes, distinct outcomes were observed in body weight modulation. Linagliptin produced a marginal, statistically non-significant weight gain (0.2 ± 0.2 kg; P = 0.349), contrasting with empagliflozin's significant weight reduction (−1.5 ± 0.4 kg; P < 0.001). The inter-group mean difference in weight change was −1.8 kg (95% CI: −2.63, −0.89; P < 0.001), underscoring empagliflozin's superior efficacy in weight attenuation. These results indicate that empagliflozin may more effectively facilitate weight management in insulin-treated patients with suboptimal glycemic control [11]. DPP-4 inhibitor, resulted in a slight, statistically non-significant increase in body weight (0.2 ± 0.2 kg; P = 0.349) when added to premixed insulin in patients with uncontrolled type 2 diabetes. This outcome suggests that linagliptin, while effective for glycemic control, does not contribute to weight reduction, indicating a neutral impact on body weight. Consequently, linagliptin may be more suitable for patients requiring stable weight alongside their glucose management.

Blood Pressure Reduction: Dipeptidyl peptidase-4 (DPP-4), an eminent protease, exerts a pivotal influence on immune modulation, inflammatory processes, oxidative stress management, cellular adhesion, and apoptosis. Its inhibitors (DPP-4i) have transcended their role as mere hypoglycemic agents to unveil substantial cardiovascular benefits, particularly in the intricate orchestration of blood pressure (BP) regulation. The mechanisms underlying these effects are multifaceted, entailing complex interplay among the nervous system, renal function, hormonal regulation, vascular dynamics, and insulin signaling. Recent inquiries have elucidated the correlation between inflammation and hypertensive states, positing that DPP-4 inhibition mitigates hypertension by enhancing immune response, attenuating inflammatory cascades, and improving oxidative stress. While DPP-4i confer modest anti-hypertensive effects as monotherapy, their efficacy is markedly amplified in synergistic regimens. Caution is advised, however, when co-administering DPP-4i with high-dose angiotensin-converting enzyme inhibitors (ACEI), as such combinations may paradoxically exacerbate BP. Ultimately, DPP-4i bolsters endothelial function and modulates BP through a confluence of mechanisms, including activation of the sympathetic nervous system and intricate modulation of the renin-angiotensin-aldosterone system (RAAS) [12]. DPP-4 inhibitors offer a promising adjunctive strategy for managing hypertension, particularly through their anti-inflammatory and oxidative stress-reducing properties. Their multifaceted mechanisms enhance vascular function and regulate blood pressure effectively. Thus, incorporating DPP-4i into therapeutic regimens may optimize cardiovascular outcomes, warranting further exploration in clinical settings.

Cardiovascular Benefits: In a detailed analysis using the JROADHF (Japanese Registry of Acute Decompensated Heart Failure), researchers investigated the cardiometabolic effects of DPP-4 inhibitors in patients with diabetes mellitus (DM) and various forms of heart failure (HF). The study included 2,999 hospitalized patients categorized into HF with preserved ejection fraction (HFpEF, n=1,130), midrange ejection fraction (HFmrEF, n=572), and reduced ejection fraction (HFrEF, n=1,297). Of these, 444, 232, and 574 patients, respectively, were treated with DPP-4 inhibitors. A multivariable Cox regression revealed that DPP-4 use significantly lowered the risk of cardiovascular death or HF rehospitalization in HFpEF patients by 31% (HR: 0.69; 95% CI: 0.55-0.87; P = 0.002), while HFmrEF and HFrEF groups showed no notable benefit.

Restricted cubic spline analysis suggested DPP-4 efficacy was more pronounced at higher ejection fractions. Propensity score matching within the HFpEF cohort (263 matched pairs) reinforced these findings, indicating a reduced incidence rate of cardiovascular death or HF hospitalization for DPP-4 users compared to non-users (19.2 vs. 25.9 events/100 patient-years; rate ratio: 0.74; 95% CI: 0.57-0.97; P = 0.027). These results highlight a potential HF phenotype-specific advantage of DPP-4 inhibitors, showing favorable outcomes predominantly in HFpEF patients [13]. The study's findings elucidate an HF phenotype-dependent stratification of DPP-4 inhibitor efficacy, indicating a pronounced cardioprotective advantage primarily within the HFpEF cohort, as evidenced by significant attenuation of cardiovascular mortality and HF readmission rates. This outcome underscores the potential of DPP-4 inhibitors to modulate cardiometabolic pathways selectively advantageous in preserved ejection contexts while remaining inconsequential in HFmrEF and HFrEF groups. Consequently, these results advocate for nuanced therapeutic strategies, tailored to the ejection fraction phenotype in HF patients with comorbid diabetes mellitus.

Renal Protection: Dipeptidyl peptidase-4 (DPP-4) inhibitors have emerged as significant therapeutic agents in the realm of diabetic kidney disease (DKD), one of the most prevalent complications stemming from diabetes mellitus, critically impacting morbidity and mortality. Emerging evidence suggests that these inhibitors possess notable antifibrotic properties, contributing to the attenuation of albuminuria and the deceleration of chronic kidney disease (CKD) progression. Linagliptin, a prominent DPP-4 inhibitor, has been shown to downregulate the advanced glycation end product (AGE) receptor, thereby alleviating the detrimental effects of oxidative stress and inflammation key factors in DKD advancement. Furthermore, the remodeling of the extracellular matrix, integral to the pathophysiology of DKD, may serve as an additional pathway through which DPP-4 inhibitors exert nephroprotective effects. Functioning within the incretin system, these agents optimize glycemic control while exhibiting multifaceted pleiotropic effects, including reducing inflammation, fibrosis, and oxidative damage, thereby indicating robust potential for renal protection [14]. Although preliminary trials suggest a possible benefit in slowing DKD progression, the existing literature lacks the necessary robustness to confirm these findings definitively. Therefore, further empirical research is warranted to elucidate the kidney-specific advantages of DPP-4 inhibitors and clarify their intricate roles in the therapeutic landscape for diabetic complications. Such studies are essential to optimize clinical strategies aimed at mitigating the renal consequences of diabetes and enhancing patient outcomes.

Safety: DPP-4 inhibitors are predominantly well-tolerated and exhibit a favorable safety profile; however, clinicians must remain cognizant of potential adverse effects. Frequently observed side effects encompass nasopharyngitis, headache, and gastrointestinal disturbances, which, although typically mild, can adversely affect patient adherence to therapy. More critical are the potential risks of pancreatitis, necessitating vigilant monitoring for symptoms such as persistent abdominal discomfort, alongside rare but notable reports of severe arthralgia and dermatological reactions. Acknowledging these safety concerns is essential for optimizing the therapeutic efficacy of DPP-4 inhibitors while mitigating associated risks in clinical practice. Furthermore, it is vital to consider individual patient factors, particularly a history of pancreatitis or hypersensitivity, to ensure safe and effective diabetes management.

In a comprehensive review by Zaresharifi, S., the dermatological adverse effects associated with dipeptidyl peptidase-4 (DPP-4) inhibitors in type 2 diabetes management were systematically analyzed to evaluate these reactions' incidence, mechanisms, and clinical management. This study revealed a diverse array of dermatological side effects, including bullous pemphigoid, severe cutaneous adverse drug reactions (SCARs), fixed drug eruptions, and various mucocutaneous manifestations. Mechanistic insights suggest these reactions may stem from autoimmune responses or inflammatory pathways activated by DPP-4 inhibition. The review also identifies patient-specific risk factors that could predispose individuals to such reactions, emphasizing the need for differential diagnosis in cases with overlapping symptoms. Additionally, the study addresses optimal management approaches, recommending

early recognition and tailored treatment strategies to mitigate adverse effects. Through this review, Zaresharifi underscores the imperative for heightened vigilance and continuous post-marketing surveillance among healthcare providers to enhance patient safety and optimize the therapeutic use of DPP-4 inhibitors in diabetic populations [15].

In a meticulous study by Huang J. to elucidate the safety profiles of dipeptidyl peptidase-4 inhibitors (DPP-4is), an extensive analysis of adverse event data was undertaken utilizing the FDA Adverse Event Reporting System (FAERS). This investigation spanned reports from 2004 Q1 to 2019 Q2, focusing on the four principal DPP-4is: sitagliptin, saxagliptin, linagliptin, and vildagliptin. Employing the advanced OpenVigil 2.1 tool, researchers meticulously calculated reporting odds ratios (RORs) alongside their corresponding confidence intervals (CIs) to identify statistically significant associations. The findings revealed that DPP-4is were disproportionately linked to critical safety concerns encapsulated within four standardized MedDRA Queries (SMQs): gastrointestinal nonspecific inflammation and dysfunction, hypersensitivity, severe cutaneous adverse reactions, and noninfectious diarrhea. Furthermore, preferred term (PT) analyses indicated heightened frequencies of adverse events involving the gastrointestinal system, pancreas, malignancies, infections, hypersensitivity, and dermatological reactions. This comprehensive examination underscores the imperative for heightened awareness among healthcare providers regarding the potential adverse effects of DPP-4is, aligning with clinical observations and contributing to a nuanced understanding of their safety profiles in diabetes management [16].

Statistical Analysis:

Software Utilized: The statistical analyses in the reviewed studies were performed using various statistical software, including [e.g., SPSS, R, or Stata], ensuring precise calculations and data management across different research.

Descriptive Statistics: The studies reported descriptive statistics, such as means, standard deviations, and ranges, for demographic characteristics (e.g., age, gender) and clinical parameters (e.g., HbA1c, fasting plasma glucose [FPG], postprandial glucose [PPG], and body weight). These statistics provided a summary of the patient populations and their baseline characteristics.

Efficacy Analysis:

Primary Outcome: Changes in glycated hemoglobin (HbA1c) from baseline to follow-up were analyzed using various methods, including [e.g., paired t-tests or mixed-effects models], as reported in the studies.

Secondary Outcomes: The proportion of patients achieving an HbA1c level of <7.0% was commonly evaluated using Chi-square tests to compare rates across different studies. Changes in FPG and PPG levels were assessed using [e.g., independent t-tests or ANOVA, as appropriate].

Safety Analysis: Adverse events, such as hypoglycemia, urinary tract infections (UTIs), genital tract infections (GTIs), acute renal failure, hypotension, and bone fractures, were summarized across studies. The frequency of these events was compared using [e.g., Fisher's exact test or Chi-square tests]. Incidences of serious adverse events were analyzed descriptively to provide an overview of the safety profile of DPP-4 inhibitors.

P-Values and Confidence Intervals: A significance level of $p < 0.05$ was commonly set for statistical tests in the included studies. Confidence intervals (CIs) were calculated for key outcomes to provide a measure of precision around estimates.

Risk of Bias Assessment: The risk of bias among the included studies was often evaluated using [e.g., the Cochrane Risk of Bias Tool], with studies categorized based on their risk of bias to enhance the reliability of the findings.

Sensitivity Analysis: Several studies conducted sensitivity analyses to assess the robustness of their results by [e.g., excluding studies with high risk of bias or varying inclusion criteria], ensuring the conclusions drawn are valid.

CONCLUSION: Dipeptidyl peptidase-4 (DPP-4) inhibitors have emerged as a pivotal class of pharmacotherapeutics in the management of type 2 diabetes mellitus (T2DM), demonstrating

significant efficacy in reducing HbA1c levels and fasting blood glucose concentrations. Their neutral influence on body weight renders them particularly advantageous for patients striving to maintain their weight while effectively controlling glycemia. Furthermore, these agents confer additional benefits beyond glycemic regulation, potentially offering cardiovascular and renal protection. However, despite their generally favorable safety profile, clinicians must remain vigilant regarding potential adverse effects, including gastrointestinal disturbances, headaches, and rare instances of pancreatitis, necessitating continuous monitoring to optimize therapeutic outcomes. In summary, DPP-4 inhibitors represent a valuable asset in diabetes management, underscoring the imperative for further investigation into their long-term effects and benefits in diverse patient populations, thereby solidifying their role as a critical component of personalized treatment strategies for T2DM.

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