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A Systematic Review and Meta-Analysis on the Efficacy and Safety of Combination Therapy with Sodium-Glucose Cotransporter Type 2 Inhibitor (SGLT2i) and Dipeptidase-4 Inhibitor (DPP4i) in Treatment of Type 2 Diabetes

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ABSTRACT

Background: The management and treatment of type 2 diabetes (T2D) remain difficult and complex, despite the wide range of pharmacotherapies available for glycemic control. As a result, researchers continue to look for new therapeutic molecules with modes of action that might fill in the gaps left by currently existing medications. The aim of this study was to assess the efficacy and safety of sodium-glucose cotransporter type2 inhibitor (SGLT2i) and dipeptidyl peptidase-4 inhibitor (DPP4i) in combination for treatment and management of type 2 diabetes (T2D).

Methods: EMBASE, MEDLINE, PUBMED and Cochrane Central Register of Controlled Trials were subjected to literature search. RCTs comparing SGLT2i plus DPP4i (SGLT2i/DPP4i) to DPP4iplacebo or SGLT2iplacebo were eligible if they were published in English and compared SGLT2i plus DPP4i (SGLT2i/DPP4i) to DPP4iplacebo or SGLT2iplacebo. The change in HbA1c from baseline was the primary endpoint.

Results: The study comprised of eight RCTs comparing SGLT2i/DPP4i and DPP4ionly, five RCTs comparing SGLT2i/DPP4i and SGLT2ionly, and three RCTs involving both comparisons. The combination of both inhibitors resulted in a greater average HbA1c reduction [WMD: 0.62 percent] than DPP4i alone, which resulted in a much lesser reduction (WMD: -0.35 percent) than SGLT2i alone. Furthermore, only SGLT2i/DPP4i vs. DPP4i revealed notable differences in body weight loss from baseline, but not SGLT2i.The risk of hypoglycemia was modest and consistent across treatment groups. Any reduction by SGLT2i/DPP4i in relation to DPP4i was proportionate to baseline HbA1c levels when patients were stratified based on baseline HbA1c levels. However, despite of baseline Hb_{A1c}, Hb_{A1c} reductions with combination were minor when compared to SGLT2i alone.

Conclusion: Combination of these two inhibitors is found to be safe and effective. A significant extra glucose-lowering impact is observed when SGLT2i is used with or added to DPP4i, but not the other way around. The extra hypoglycemic effects of SGLT2i in combination with DPP4i were assessed by baseline HbA1c.

Keywords: Efficacy, safety, DPP4i, SGLT2i, Treatment, Type 2 Diabetes

INTRODUCTION

Despite the availability of several pharmacotherapies for the management of

type 2 diabetes (T2D), management and treatment remain difficult and complex, according to a paper from 2017 [1]. As a result, researchers continue to look for new therapeutic molecules with modes of action that might fill in the gaps left by currently existing medications. While there are a number of cutting-edge treatments for T2D in development, sodium-glucose cotransporter type 2 inhibitors (SGLT2is) and dipeptidyl peptidase-4 inhibitors (DPP4is) are the most current antihyperglycemic medications [2]. By increasing insulin production and decreasing glucagon secretion from pancreatic b-cells and a-cells, respectively, DPP4 aids in blood glucose regulation. As a result, endogenous glucose production (EGP) is reduced [3, 4].

Some RCTs claim that DPP4 inhibitors, when used as monotherapy, reduce HbA1c by an average of 0.6-0.7% (6.6-7.6 mmol/mol), with a minimal risk of hypoglycemia and weight neutrality [5,6, 7]. SGLT2 reduces plasma glucose levels by decreasing renal glucose reabsorption and increasing urine glucose excretion, resulting in a negative energy balance and a weight loss of 2-4 kg [8, 9]. Until co-administered with insulin or insulin secretagogues, SGLT2i alone improves glucose control with a 0.5–1.0 percent (5.4–10.9 mmol/mol) decrease in HbA1c [4, 10, 11] and a low risk of low glucose levels [12]. Because of their complementary mechanisms of action, SGLT2i and DPP4i work well together to treat a number of pathophysiological illnesses [13]. Compared to utilising either component alone, certain studies have demonstrated that SGLT2i/DPP4i treatment can significantly improve glycemic control [14,15]. We aimed to assess the efficacy and safety of sodium-glucose cotransporter type2 inhibitor (SGLT2i) and dipeptidyl peptidase-4 inhibitor (DPP4i) in combination compared with DPP4i vs SGLT2i vs Placebo for treatment and management of type 2 diabetes (T2D).

METHODS

A PRISMA Checklist was adopted for the study and to identify eligible studies searches were conducted on Cochrane Library databases, Embase and PubMed from the inception of the review to 1st June, 2022.

The design for this review investigated strictly RCTs where the safety and efficacy of SGLT2i and DPP4i were examined in a combined treatment.

Studies with at least 12 weeks follow up period and published in English language were considered for inclusion after screening of abstracts and full texts of studies.

The search strategy is presented below in Table 1.

Search Terms	Joining Type	Database	Field to be Searched
Efficacy of SGLT2i/ DPP4i	N/A	Medline, PubMed Embase,	All fields
Efficacy	N/A	Medline, PubMed Embase	All fields
Safety	N/A	Medline, PubMed, Embase	All fields
SGLT2i	N/A	Medline, PubMed, Embase	All fields
DPP4i	N/A	Medline, PubMed, Embase	All fields
#1, #2, #3, #4, #5	AND	Medline, PubMed, Embase	N/A
Placebo	N/A	Medline, PubMed, Embase	All Fields
#6, #7	AND	Medline, PubMed, Embase	All fields
Randomized Control Trials	N/A	Medline, PubMed, Embase	All fields
#8, #9	AND	Medline, PubMed, Embase	N/A

Data Extraction

Examining the fluctuation in Hb_{A1c} from the beginning to the conclusion of each included trial was the research's main goal. The number of people achieving the treatment goal of a Hb_{A1c} of less than 7.0 percent (53.0 mmol/mol), variation in body weight, fasting plasma glucose (FPG), and the risk of hypoglycemia at the same time point as the primary endpoint were among the secondary factors. For each research, the author, year of publication, background therapy, body mass index, baseline Hb_{A1c}, and length of treatment were also retrieved.

Methodological Quality Assessment

Data analysis was performed using RevMan software. Cochran collaboration risk of bias tool was used in assessing the risk of bias in the included studies. Consolidated approximates of the weighted mean difference (WMD) and95% confidence intervals (CIs) were calculated for continuous variables, such as FPG, variation in Hb_{A1c}, systolic blood pressure, body weight, along with consolidated risk ratios and their 95% CIs for discrete variables, such as the number of individuals achieving target Hb_{A1c}, and risks of hypoglycemia. A random-effects model was used to aggregate the studies, and forest plots were generated to summarize the results. I^2 statistics were used to measure statistical heterogeneity between studies. The publication bias was assessed by developing funnel plots of the primary result combined with asymmetry measured via Egger's test. To study heterogeneity, subgroup analyses of Hb_{A1c}deductions were calculated, with a baseline Hb_{A1c} level of 8.0–8.5 percent (63.9–69.4 mmol/mol) as the cut off.

After an extensive search, a total of 649 studies were identified. After screening for eligibility, ten RCTs reporting the primary aim of this study were included. Eight RCTs involved a total of 2220 diabetic patients that investigated the safety and efficacy of SGLT2i/DPP4i combined versus DPP4i and five others investigated safety and efficacy of SGLT2i/DPP4i combined versus SGLT2i. From the Meta analyses included three RCTs compared both SGLT2i/DPP4i vs. DPP4i and SGLT2i/DPP4i vs SGLT2i [16,15,14]. The efficacy and safety of combination therapy vs. DPP4i or SGLT2i alone in metformin-treated (1500 mg/day) [14, 16]or treatment-naïve [15]patients with T2D were assessed in these trials. The extra efficacy and safety of SGLT2i [17,18,19, 20, 21]or DPP4i [22, 23]were compared to the same dose of placebo in metformin-treated (1500 mg/day) [22,17,18; 20,21] or single-component-treated T2D patients (DPP4i for the SGLT2i add-on trials and SGLT2i for the DPP4i add-on trials) [18]. The PRISMA flow chart for the study is represented below in Figure 1 and Baseline characteristics of included studies in Meta analysis in Table 1.

RESULTS

Table 1: Included studies characteristics

Studies	Therapy	Age (Years)	Patients (n)	Duration (Weeks)	FPG (mg/dL)	BMI (Kg/m^2)	Male (%)	HbA_{ic} (%)	HbA_{ic} (mmol/mol)
[20]	Metformin + sitagliptin 100mg	57.4 57.5	107 106	26	185.5 180.4	32.3 31.7	61.7 51.9	8.5 8.4	69.4 68.3
[18]	Teneligliptin 20mg	58.4 56.0	70 68	24	173.9 166.3	25.5 26.4	77.1 77.9	8.2 7.9	65.9 62.5
[23]	Metformin + dapagliflozin 10mg	54.7 54.5	153 162	24	164.0 158.0	31.4 31.4	47.7 46.9	8.0 7.9	63.6 62.4
[16]	Metformin	57.1 55.5 56.2	134 140 128	24	154.6 159.9 156.3	30.6 31.8 30.6	53.7 46.4 50.0	7.9 8.0 8.0	62.8 64.2 64.2
[19]	Metformin+Saxagliptin 5mg	55.2 55.0	160 160	24	179.0 177.0	31.2 32.2	43.7 47.5	8.2 8.2	66.6 65.8
[22]	Metformin + empagliflozin 10mg	56.6 56.8	122 125	24	159.5 157.1	31.3 30.8	56.6 56.0	8.0 8.0	64.4 64.3
[22]	Metformin + empagliflozin 25mg	56.6 56.1	110 110	24	152.1 155.4	30.8 32.0	47.3 57.3	7.8 7.9	61.9 62.6
[14]	Metformin	53 54 55	179 179 176	24	180.0 192.0 185.0	31.8 31.8 31.5	47 53 50	8.9 9.0 8.9	74.0 75.2 73.4
[21]	Metformin + Linagliptin 5mg	55.4 55.9	110 108	24	169.2 163.8	29.9 29.6	64.5 55.6	8.0 8.0	63.6 63.6
[17]	Metformin + sitagliptin 100mg	54.8 55.0	223 224	24	162.2 163.0	NR NR	57.0 52.7	7.9 8.0	62.8 63.9
[15]	Empagliflozine ++	54.2 56.0 53.8	134 133 133	24	156.1 152.8 156.0	31.8 31.2 31.9	52.2 57.9 56.4	8.0 8.0 8.1	63.8 63.8 64.5

***FPG: Fasting Blood Glucose, NR: Not reported, BMI Body Mass Index Hb_{A1c}: haemoglobin A_{1c};**

****The study by [22] consisted of two different trials of linagliptin 5mg intervention (Metformin + empagliflozin 25mg) and placebo conducted 6weeks apart***

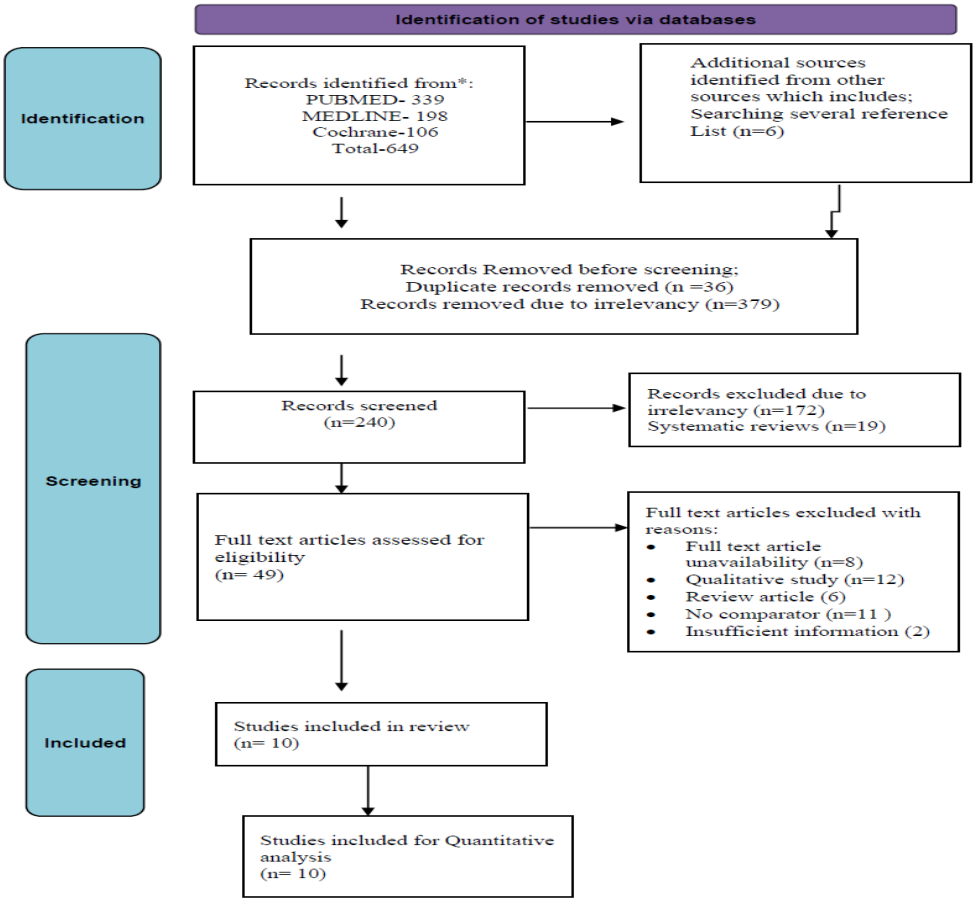

Figure 1; PRISMA Flow Chart for the Study

Efficacy

Figure 2 below shows the results of eight RCTs comparing SGLT2i/DPP4i to DPP4i [14, 15, 16, 17,18, 19, 20, 21], The combination was linked to a considerably lower HbA1c level than DPP4i alone (WMD: 0.62 percent, 95 percent CI: 0.73-0.51 percent; P<0.001). In addition, when SGLT2i was combined to DPP4i (WMD: 0.70%, 95%CI: 0.85 0.54%; P<0.001), the reduction in HbA1c was slightly higher (WMD: 0.51%, 95% CI: 0.65 -0.37%; P<0.001) than when SGLT2i/DPP4i was used alone (WMD: 0.51%, 95% CI: 0.65 - 0.37 percent; P<0.001).

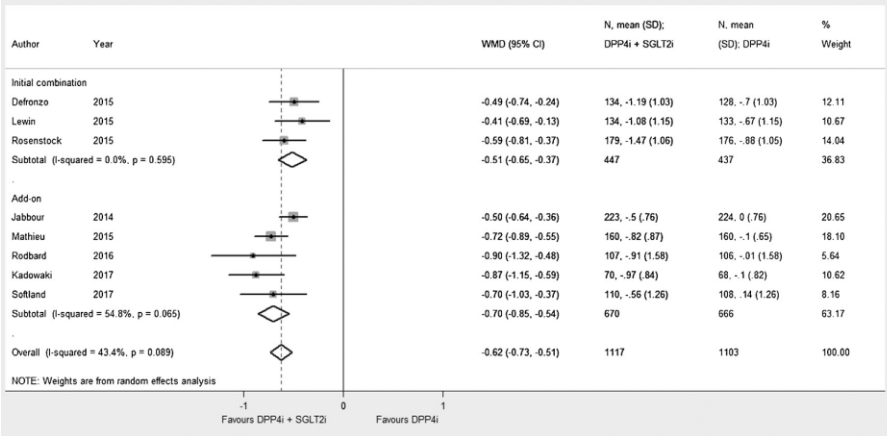

Figure 2: Weighted Mean Difference between SGLT2i/DPP4i compared to DPP4i in terms of changes in baseline HbA_{ic}levels (%)

Figure 3 from the meta-analysis of the five RCTs comparing SGLT2i/DPP4i to SGLT2i/DPP4i [14, 15, 16, 22, 23], in comparison to SGLT2i alone, the combination was linked with a considerably greater decrease in HbA1c (WMD: 0.35%, 95% CI: 0.48-0.22%; p<0.001). When the HbA1c reduction was further examined, the initial combination (WMD: 0.32%, 95% CI: 0.58-0.06%; p=0.016) and DPP4i as an add-on treatment to SGLT2i (WMD; 37%, 95% CI: 0.50-0.25 percent; p=0.001) showed similar results. No noticeable uneven distribution or small-study effect was found using funnel plots and Egger's regression test. This result did not indicate any publication bias regardless of the few available studies and moderate diversification.

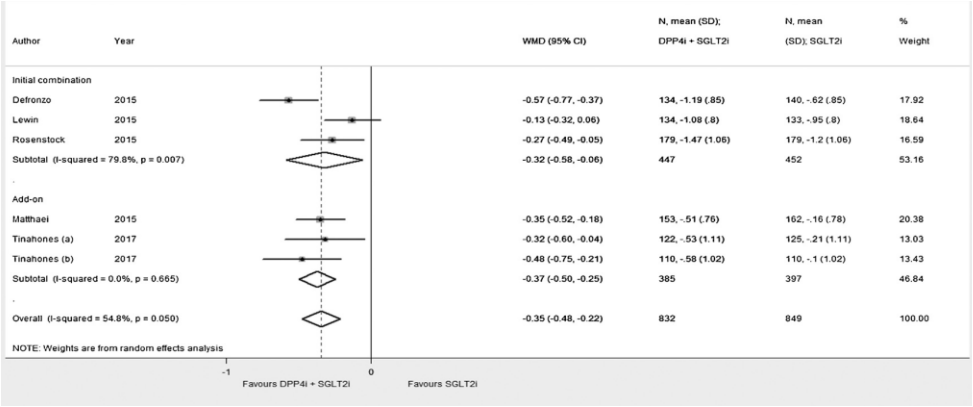

Figure 3: Weighted Mean Difference between SGLT2i/DPP4i compared to SGLT2i in terms of changes in baseline HbA_{ic}levels (%).

Figure 4 displays baseline variations in FPG as determined by eight RCTs of DPP4i vs. SGLT2i/DPP4i (n = 2220) [14, 15, 16, 17,18, 19, 20,21] and five RCTs of SGLT2i/DPP4i vs. SGLT2i (n = 1681) [15, 16,14,22,23]. SGLT2i/DPP4i reduced FPG substantially more than DPP4i alone (WMD: 28.30 mg/dL, 95% CI: 32.31-24.28 mg/dL; p<0.001). From figure 4 lower this was true when the two inhibitors were mixed sequentially (WMD: 31.29 mg/dL, 95% CI: 36.18-26.39 mg/dL; p<0.001) or concurrently (WMD; 23.42 mg/dL, 95% CI: 28.77-18.08 mg/dL; p<0.001).

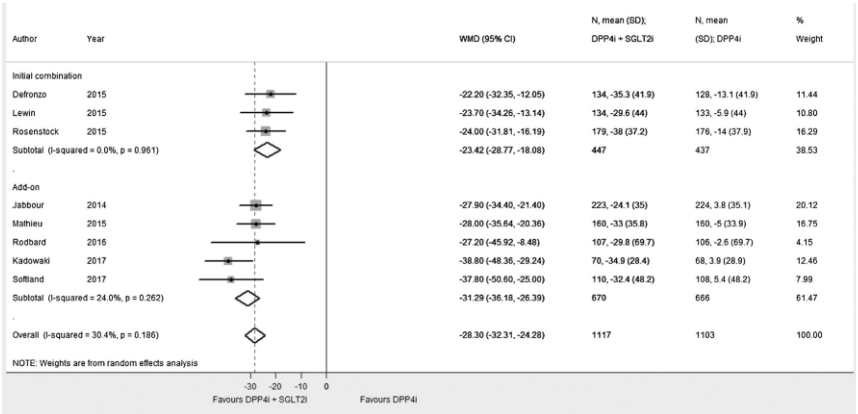

Figure 4: Weighted Mean Difference between SGLT2i/DPP4i compared to DPP4i in terms of changes in fasting glucose levels (mg/dL)

SGLT2i/DPP4i reduced FPG significantly more than SGLT2i alone (WMD: 7.47 mg/dL, 95 percent CI: 11.01-3.92 mg/dL; p<0.001), irrespective of whether they were combined stepwise (WMD: 6.63 mg/dL, 95% CI: 12.05-1.21 mg/dL; p<0.001) or simultaneously (Except for [17] in their study of SGLT2i/DPP4i combined to

DPP4i). Regardless of the method of combination, the difference was large. The changes in body weight from baseline were measured in all RCTs. Weight reduction from baseline was significantly different with SGLT2i/DPP4i vs. DPP4i (WMD: 1.75 kg, 95% CI: 2.02-1.49 kg; p= 0.001), but not with SGLT2i (WMD: 0.29 kg, 95% CI: 0.14-0.71 kg; p<0.191), and the outcome was identical in despite of how SGLT2i and DPP4i were. Four studies comparing DPP4i to SGLT2i/DPP4i and other four comparing DPP4ito SGLT2i [14, 15,16,17]. and four studies comparing SGLT2i to DPP4i [14, 15, 16, 23] both showed Hb_{A1c} reductions based on baseline values.

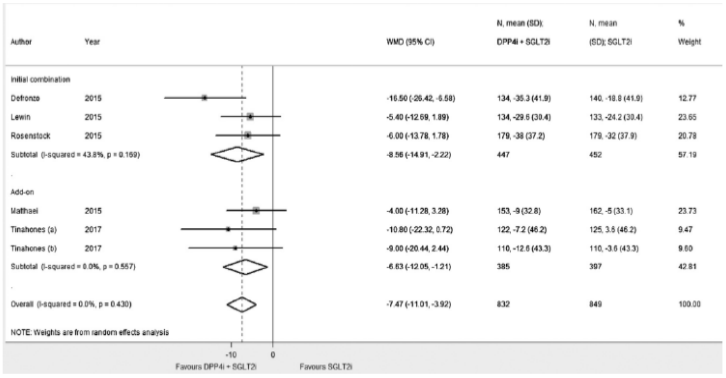

Figure 5: Weighted Mean Difference between SGLT2i/DPP4i compared to SGLT2i in terms of changes in fasting glucose levels (mg/dL)

Safety

Even though all of the RCTs reviewed reported the number of low glucose levels scenarios, the two studies in which their arms using background therapy with empagliflozin 10 mg reported no such events between the two groups, they were excluded from the combined RR calculation [18,22]. In terms of genital infections, every RCT reported the number of cases. SGLT2i/DPP4i had a substantially higher risk of genital infection than DPP4i (RR: 2.94, 95%CI: 1.23-7.00; p=0.015), while SGLT2i/DPP4i had a lower combined RR than SGLT2i alone (RR: 0.42, 95% CI: 0.18 to 0.99; p=0.046).

DISCUSSION

The effectiveness and safety of a combination therapy using SGLT2i and DPP4i for the treatment of T2D were assessed in this research. With a minimal risk of hypoglycemia, this combination led to clinically substantial reductions in HbA1c and FPG values. The results of this study demonstrated that the hypoglycemic effects of SGLT2i in combination with DPP4i are determined by baseline HbA1c. Furthermore, this study found that the glycemic control was remarkable when SGLT2i was combined with or added to DPP4i, rather than the other way around, as suggested in a review [13].[2] highlighted that to address hyperglycemia; the increasing decline of b-cell activity in T2D frequently necessitates combined therapy. The ideal glucose-lowering pharmaceutical combination has to have complementary physiological pathways and solid safety profiles with low risks of hypoglycemia, weight gain, and cardiovascular events [24, 25,26]. These inhibitors' chemical treatment is highly intriguing since it uses many modes of action to address various pathophysiological problems connected to type 2 diabetes [8, 13]. Additionally, studies by [27, 28] shown that when both medication classes have a favourable weight profile, they must be coupled and exhibit acceptable tolerability. Three RCTs assessed the effectiveness and safety of the first SGLT2i/DPP4i combination with SGLT2i or DPP4i alone in patients receiving metformin [16, 14] or receiving no treatment for type 2 diabetes (T2D) [15]. This study found that the extra HbA1c

decrease by DPP4i was considerable regardless of baseline HbA1c (Figure 2). One reason for this discovery might be because the use of SGLT2i causes compensatory increases in glucagon and EGP levels [29, 30]. [31] believed it is probable that the EGP stimulation caused by SGLT2i-induced glycosuria is so high that it overpowers DPP4i's benefits since DPP4i decreases blood glucose levels by blocking EGP and reducing glucagon production. In contrast, the principal mechanism of SGLT2i is enhanced renal glucose excretion, therefore the administration of DPP4i is less likely to affect its effect. In light of this, SGLT2i may have hypoglycemic effects without the use of DPP4i.Additionally, it has been discovered that DPP4i has a stronger influence on the clinical efficacy of SGLT2i than does higher baseline HbA1c [32, 16]. The results of this study suggest that SGLT2 and DPP4 seldom result in hypoglycemia, which is consistent with their well-known safety profiles. This study has some limitations, such as the various HbA1c definitions. Second, the studies' hypoglycemia criteria were varied, and they neglected to examine important safety issues such euglycemic ketoacidosis as well as the long-term implications of T2D. Despite these obstacles, there aren't many studies evaluating the efficacy and safety of SGLT2i/DPP4i combined, which would contribute to the body of knowledge and help guide decision-makers about the effectiveness of combination treatment in the management of type 2 diabetes.

CONCLUSION

These two inhibitors work well together and have been confirmed to be safe. However, when SGLT2i is administered in conjunction with or added to DPP4i, a considerable additional glucose-lowering effect is shown, but not the other way around. Additionally, baseline HbA1c levels significantly influenced the antihyperglycemic effects of SGLT2i in addition to DPP4i, indicating that additional study is necessary to fully understand this effect's mechanism.

Ethical Approval & Consent to Participate: Not applicable

Consent to Publish: Not applicable

Availability of Data and Materials: The Data set from the study are available to the corresponding author upon request.

Acknowledgement: None

Conflict of Interest: Authors have declared that they have no competing interest.
Source of Funding: None

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