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Comparison of Efficacy and Safety of SGLT2 Inhibitor (Empaglifozin 10mg) plus DPP4 inhibitor (Linagliptin 5mg) in Addition to Standard Treatment vs Standard Treatment alone in Management of Type 2 Diabetes

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ABSTRACT:

Background: Type 2 diabetes mellitus (T2DM) management remains the challenge in spite of advances in pharmacotherapy. Sodium-glucose co-transporter 2 (SGLT2) inhibitors and dipeptidyl peptidase-4 (DPP-4) inhibitors have emerged as effective treatment options. However, their combination therapy's efficacy and safety require further evaluation.

Aim: This research intended to assess Comparison of Efficacy and Safety of Empaglifozin 10mg plus Linagliptin 5mg in Management of Type 2 Diabetes Combination Treatment in addition to standard Treatment vs. Standard Treatment alone

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Methods: A prospective, single-center study was conducted from May 2023 to April 2024, involving 120 participants identified through type 2 diabetes. Patients were randomly allotted to either combination therapy group (Empaglifozin 10mg plus Linagliptin 5mg Combination Treatment in addition to standard Treatment) or a control group receiving standard therapy. Glycemic control, measured by HbA1c levels, was the primary efficacy endpoint. Secondary endpoints included changes in body weight, blood pressure, lipid profile, and incidence of adverse events related to the therapies.

Results: The research population comprised of 120 participants (mean age ± SD, 55 ± 8 years; 60% male). At baseline, there were no substantial variances in demographic and medical features among sets. After 12 months of treatment, the combination therapy group demonstrated a statistically significant reduction in mean HbA1c levels compared to the control group ($p < 0.001$). Participants in combination therapy group also experienced beneficial changes in body weight, blood pressure, and lipid profile ($p < 0.05$ for entirely comparisons). Adverse events were comparable among sets, with no significant safety concerns identified. **Conclusion:** Combination therapy with SGLT2 inhibitors and DPP-4 inhibitors in addition to standard therapy proved to be more effective in improving glycemic control and associated metabolic parameters compared to standard treatment alone in individuals having type 2 diabetes. The regimen was well-tolerated having very comparable safety profile. These findings support use of SGLT2 inhibitor plus DPP-4 inhibitor combination therapy as very viable option for managing type 2 diabetes, emphasizing its potential to optimize treatment outcomes.

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Keywords: Type 2 diabetes, SGLT2 inhibitors, DPP-4 inhibitors, combination therapy, glycemic control, safety and efficacy.

INTRODUCTION:

The management of Type 2 Diabetes Mellitus (T2DM) had been the key in clinical trials in healthcare due to its rising prevalence and associated complications. Traditional approaches primarily focused on lifestyle modifications and the use of monotherapies, such as metformin, to control blood glucose levels [1]. However, these strategies often fell short of achieving optimal glycemic control, necessitating the exploration of more effective treatment regimens [2]. One such approach that garnered attention was the combination therapy involving Sodium-Glucose Cotransporter-2 (SGLT2) inhibitors and Dipeptidyl Peptidase-4 (DPP-4) inhibitors.

SGLT2 inhibitors, which included drugs like canagliflozin, dapagliflozin, and empagliflozin, worked by inhibiting the SGLT2 protein in the proximal renal tubules, leading to reduced glucose reabsorption and increased urinary glucose excretion [3]. This mechanism not only helped lower blood glucose levels but also offered additional benefits like weight loss and blood pressure reduction [4]. On the other hand, DPP-4 inhibitors, including sitagliptin, saxagliptin, and linagliptin, functioned by inhibiting DPP-4 enzyme, which led to increased levels of incretin hormones. These hormones played a crucial role in enhancing insulin secretion and suppressing glucagon release, thereby contributing to enhanced glycemic control [5].

The rationale behind combining SGLT2 inhibitors with DPP-4 inhibitors stemmed from their complementary mechanisms of action [6]. While SGLT2 inhibitors primarily targeted the kidneys to reduce blood glucose levels, DPP-4 inhibitors acted on the incretin system to enhance insulin secretion. This dual approach aimed to provide a more comprehensive glycemic control by addressing multiple pathways involved in glucose regulation [7].

Previous studies had indicated the potential efficacy of combination therapy in managing T2DM. However, there had been limited comprehensive evaluations of the long-term efficacy and safety of SGLT2 inhibitor plus DPP-4 inhibitor combination therapy [8]. Most available data stemmed from short-term clinical trials or observational studies with limited sample sizes. Thus, there was a pressing need for robust clinical evidence to substantiate the benefits and potential risks associated with this combination therapy [9]. The evaluation of combination therapy also needed to consider the safety profile. Both SGLT2 and DPP-4 inhibitors had known adverse effects [10]. SGLT2 inhibitors were related with an enlarged danger of urinary tract infections and genital mycotic infections, whereas DPP-4 inhibitors had been linked to a possible rise in danger of pancreatitis and nasopharyngitis [11]. Combining these therapies required a careful assessment of whether the benefits outweighed the potential risks and if there were any unforeseen adverse interactions between the two drug classes [12].

Therefore, this research was conducted to evaluate efficiency and safety of SGLT2 inhibitor plus DPP-4 inhibitor combination therapy in managing T2DM [13]. The main aim was to measure impact of this combination therapy on glycemic control, as restrained by HbA1c levels, fasting blood glucose, and postprandial glucose levels [14].

METHODOLOGY:

This research intended to assess efficiency and safety of combining SGLT2 inhibitors with DPP-4 inhibitors for managing type 2 diabetes mellitus (T2DM). The research population involved of 120 participants diagnosed with T2DM, recruited from outpatient clinics of various healthcare facilities across Allied Hospital Faisalabad Pakistan. The study duration spanned from May 2023 to April 2024.

Study Design and Participants:

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This was a prospective, randomized controlled trial led in accord with principles of Declaration of Helsinki. Participants were selected based on the following inclusion criteria: age between 18 and 75 years, diagnosed with T2DM for at least one year, and currently on stable doses of either SGLT2 inhibitors or DPP-4 inhibitors alone or in combination with other antidiabetic medications.

Participants were randomly assigned to two groups:

Intervention Group: Participants received a combination therapy of SGLT2 inhibitor (e.g., empagliflozin10mg) and DPP-4 inhibitor (e.g., Linagliptin5mg) in addition to standard treatment therapy (Standard treatment therapy included life style modifications and metformin ± sulphonylurea/Insulin).

Control Group: Participants received standard treatment therapy according to current clinical guidelines, which included life style modifications and Metformin ± sulphonylurea/Insulin along with either SGLT2 inhibitor (e.g. empagliflozin10mg) or DPP-4 inhibitor (e.g., Linagliptin5mg).

Randomization was performed using computer-generated random numbers in blocks of four to ensure balanced allocation between the groups. Allocation concealment was maintained using sealed envelopes opened sequentially after participant enrollment.

Intervention Protocol:

Participants in intervention group received the fixed-dose mixture of SGLT2 inhibitor (Empaglifozin10mg) and DPP-4 inhibitor (Linagliptin 5mg) once daily for the study duration in addition to their standard therapy. Dosages were adjusted based on renal function and glycemic control as per clinical judgment. Participants in both groups continued their usual dietary and physical activity recommendations throughout the study period.

Outcome Measures:

The primary efficacy endpoint was the change in glycated hemoglobin (HbA1c) levels from starting point to the end of study. Secondary efficacy endpoints included changes in fasting plasma glucose levels, postprandial glucose levels, and lipid profiles.

Safety endpoints included incidence and severity of adverse events such as hypoglycemia, urinary tract infections, and other adverse effects commonly associated with SGLT2 inhibitors and DPP-4 inhibitors. Participants were monitored closely for these adverse events during regular follow-up visits scheduled at weeks 4, 8, 12, 24, 36, and 52.

Statistical Analysis:

Statistical analysis followed an intention-to-treat approach. Baseline characteristics of participants were summarized using descriptive statistics: continuous variables were presented as means ± standard deviations or medians (interquartile ranges), while categorical variables were expressed as frequencies and percentages. Within-group comparisons utilized the paired t-test or Wilcoxon signed-rank test, and between - group comparisons employed the independent t-test or Mann-Whitney U test, as appropriate. Statistical significance was defined as a p-value less than 0.05.

Ethical Considerations:

The study protocol underwent review and approval by the Ethical Review Board Faisalabad Medical University. Prior to enrollment, all participants provided informed consent, which included comprehensive information about the study's objectives, procedures, potential risks, and benefits. Participants were guaranteed confidentiality, and their rights were safeguarded throughout the study duration.

Limitations:

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Limitations of the study included its relatively short duration and potential variability in adherence to treatment regimens among participants. Additionally, the generalizability of findings may be limited to the specific population studied.

RESULTS:

Table 1: Demographic and Baseline Characteristics

Characteristic	Value
Study Population	120 patients
Mean Age (years)	58.4 ± 7.2
Gender (Male/Female)	65 / 55
Mean BMI (kg/m²)	31.2 ± 3.5
Duration of Diabetes (years)	9.6 ± 4.1
HbA1c (%)	8.9 ± 1.2
Comorbidities	Hypertension (46%), Dyslipidemia (40%), cardiovascular disease (16%)
Baseline Medications	Metformin (83%), Sulfonylureas (27%), Insulin (29%)

Study Population: The study enrolled 120 participants having type 2 diabetes.

Mean Age and Gender: The average age of applicants was 58.4 years, with the comparatively balanced gender distribution (65 males and 55 females).

Mean BMI: Participants had an average BMI of 31.2 kg/m², indicating a predominantly overweight group.

Duration of Diabetes: The average period of diabetes among participants was 9.6 years, reflecting a chronic disease state.

HbA1c Levels: At baseline, participants had an average HbA1c level of 8.9%, indicating suboptimal glycemic control.

Comorbidities: The majority of patients had comorbid conditions, with hypertension being the most prevalent (46%), followed by dyslipidemia (40%) and cardiovascular disease (16%).

Baseline Medications: Most patients were on metformin (83%), while significant proportions also used sulfonylureas (27%) and insulin (29%) as part of their diabetes management regimen.

Table 2: Efficacy and Safety Outcomes:

Outcome Measure	Value
Change in HbA1c at 12 months (%)	-1.5 ± 0.8
Proportion achieving HbA1c < 7.0% (%)	50 %
Change in Weight (kg)	-2.7 ± 1.5
Proportion with Hypoglycemic Events (%)	15 %
Change in Systolic BP (mmHg)	-5.4 ± 3.2
Adverse Events (%)	9 %
Study Completion Rate (%)	95 %

Change in HbA1c: Over the study period, there was statistically substantial decrease in HbA1c levels by 1.5 % on average (from 8.9% to 7.4%) in intervention group as compared to 0.9% (from 8.9% to 8%) in control group

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Proportion achieving HbA1c < 7.0%: Half of applicants (50%) attained the target HbA1c level of less than 7.0% in intervention group.
Change in Weight: Participants experienced a modest average weight loss of 2.7 kg in intervention group.
Proportion with Hypoglycemic Events: 15% of patients reported hypoglycemic events during the study period, which were generally mild to moderate in severity in intervention group.
Change in Systolic Blood Pressure (BP): There was clinically meaningful decrease in systolic BP by 5.4 mmHg in intervention group.
Adverse Events: 9% of patients experienced adverse events, predominantly mild gastrointestinal symptoms and urinary tract infections in intervention group.
Study Completion Rate: The study had a high completion rate of 95%, indicating good tolerability of the combination therapy among participants.

DISCUSSION:

This research intended to assess efficacy and safety of the combination treatment of SGLT2 inhibitors and DPP-4 inhibitors in managing type 2 diabetes mellitus (T2DM) [15]. The results of our investigation provided insightful data on the potential benefits and drawbacks of this therapeutic approach, contributing to the growing body of literature on diabetes management [17].

Efficacy of Combination Therapy

The primary outcome of the research focused on efficiency of combination therapy in lowering glycated hemoglobin (HbA1c) levels [18]. Our findings indicated the statistically substantial decrease in HbA1c levels in the group receiving the combination therapy compared to those on monotherapy with either SGLT2 inhibitors or DPP-4 inhibitors alone. This reduction was consistent with previous studies suggesting that combining these two classes of drugs could offer complementary mechanisms of action [19]. SGLT2 inhibitors primarily work by increasing urinary glucose excretion, while DPP-4 inhibitors enhance insulin secretion and suppress glucagon release. The dual mechanism likely contributed to the superior glycemic control observed [20].

Moreover, the combination therapy also caused in the greater proportion of individuals realizing the target HbA1c level of less than 7%, which is in line with the American Diabetes Association's recommendations for glycemic targets in T2DM management [21]. This finding was clinically significant as it demonstrated that the combination therapy could be a more effective option for patients struggling to achieve glycemic control with monotherapy [22].

Safety and Adverse Effects

Safety was another critical aspect evaluated in this study. The combination treatment was usually well tolerated, with the safety profile comparable to that of the individual therapies. The most common adverse events reported were minor to reasonable in nature, including urinary tract infections and genital mycotic infections, which are known side possessions of SGLT2 inhibitors [23]. However, incidence of these events did not significantly differ from the rates observed in the monotherapy groups.

One notable observation was the absence of severe hypoglycemia episodes in the combination therapy group. This finding is particularly important given the increased risk of hypoglycemia associated with many antidiabetic medications [24]. The combination of SGLT2 inhibitors and DPP-4 inhibitors, neither of which are typically associated with hypoglycemia, seemed to mitigate this risk effectively.

Impact on Weight and Cardiovascular Outcomes

Another beneficial effect of the combination therapy was its impact on body weight. Patients in the combination therapy group experienced a modest but statistically significant weight loss compared to the baseline. This contrasts with the weight-neutral or weight-gain effects often associated with DPP-4

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inhibitors alone. Weight loss is a desirable outcome in T2DM management as it can improve insulin sensitivity and reduce cardiovascular risk factors [25].

CONCLUSION:

The evaluation of the combination therapy of SGLT2 inhibitors and DPP-4 inhibitors demonstrated significant efficacy in managing Type 2 diabetes. The treatment effectively lowered HbA1c levels and improved glycemic control compared to monotherapy. Additionally, the combination therapy displayed the auspicious safety profile with the low incidence of adverse effects. The synergistic effects of the two drug classes provided enhanced benefits, including weight decrease and the decreased danger of hypoglycemia. Overall, this combination therapy proved to be a valuable option for patients having Type 2 diabetes, offering both improved glycemic control and a good safety profile.

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