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Efficacy of Sodium-Glucose Transport Protein 2 Inhibitors (SGLT-2) and Dipeptidyl Peptidase 4 (DPP-4) Inhibitor in Weight Reduction in Patients with Type II Diabetes Mellitus

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ABSTRACT

Objectives: to compare the efficacy of sodium-glucose cotransporter 2 (SGLT-2) inhibitors and dipeptidyl peptidase-4 (DPP-4) inhibitors in achieving weight reduction among patients newly diagnosed with type 2 diabetes mellitus (T2DM). **Study Settings** Department of Medicine, Aziz Fatimah Hospital, Faisalabad. **Duration of Study:** This randomized controlled trial was conducted over a period of six months following approval from the Institutional Ethical Review Committee. **Data Collection:** A total of 60 patients (30 in each group) were enrolled using non-probability consecutive sampling. The SGLT-2 inhibitor group received empagliflozin (10 mg once daily), while the DPP-4 inhibitor group received sitagliptin (50 mg once daily), in addition to their usual diabetic treatment. The primary outcome was achieving ≥3% weight reduction over 12 weeks. **Results:** The mean weight reduction percentage in the SGLT-2 inhibitor group was 4.72% ± 0.74%, significantly higher than in the DPP-4 inhibitor group (1.78% ± 1.12%, $p<0.001$). A remarkable higher proportion of patients in the SGLT-2 inhibitor group (88.1%) achieved ≥3% weight loss compared to the DPP-4 inhibitor group (11.9%, $p<0.001$). **Conclusion:** Significant efficacy was recorded in SGLT-2 inhibitors while achieving weight reduction in newly diagnosed T2DM patients compared to DPP-4 inhibitors.

INTRODUCTION

The burden of type 2 diabetes mellitus (T2DM) is rapidly increasing as urbanization and economic growth continue to accelerate. It is a chronic disease affecting a significant portion of the global population. According to reported statistics from the International Diabetes Federation (IDF), around 425 million adults between age range of 20–79 (8.8%) have diabetes, with numbers projected to reach 629 million by the years 2045. In developed nations, T2DM accounts is recorded from 87% to 91% of diabetics.[1-2]

Obesity, dyslipidemia and high blood pressure are responsible as a significant but modifiable causative factor for development of T2DM. When these metabolic conditions exist together in the individuals, which is a common scenario, they do not just add to the risk of cardiovascular complications—they amplify it.[3] Various individuals with T2DM manage to meet their glycemic targets; however, this may lead to unintended consequences like weight gain and a greater likelihood of severe hypoglycemia. These risks are especially correlated with insulin therapy, which is known for its side effects of weight gain and hypoglycemia. Management of weight is a fundamental part of T2DM treatment, as it improves insulin sensitivity and helps to regulate blood glucose levels.[4] Even a low reduction in body weight (5%–10%) can increase metabolic control and reduce cardiovascular risk factors. Despite variety of anti-diabetic medications available, maintaining and achieving an optimal balance between glycemic control and weight reduction remains a challenging goal.[5]

Widely used for managing T2DM, sodium-glucose cotransporter 2 (SGLT2) inhibitors and dipeptidyl peptidase-4 (DPP-4) inhibitors have been extensively studied for their effects on weight loss.[6] Research indicates that SGLT2 inhibitors can lead to weight reductions of approximately 1 to 4 kg, although differences in drug type and dosage may influence these outcomes. Son C et al[7] conducted a comparison of the efficacy of canagliflozin (an SGLT2 inhibitor) and

teneligliptin (a DPP-4 inhibitor) in managing three metabolic risk factors—hypertension, obesity, and dyslipidemia—in Japanese patients with T2DM. A considerably higher percentage of patients in the canagliflozin group had a reduction in body weight by 3% when compared to the teneligliptin group (55.9% vs. 10.5%, $p < 0.0001$).

Numerous studies have shown that SGLT-2 inhibitors are associated with hemoglobin A1c lowering when they are used alone or in combination with other therapy. Evidence also supports that these medications assist in decreasing systolic blood pressure, fasting blood glucose levels, and also in weight reduction.[8] Other systematic reviews and meta-analyses conducted in the recent past have shown that DPP-4 inhibitors are safe for use in diabetic patients and have the additional advantage of weight loss.[9-11] The present study is intended to evaluate the efficacy of these two classes of medications in inducing weight loss in individuals newly diagnosed with Type 2 Diabetes Mellitus.

The study aimed to analyze the impact of an SGLT2 inhibitor and a DPP-4 inhibitor on weight loss in patients with T2DM. Identifying the superior drug will aid in future recommendations for optimizing treatment and enhancing glycemic control in diabetic patients.

METHODOLOGY

This randomized controlled trial was conducted at the Department of Medicine, Aziz Fatimah Hospital, Faisalabad, over a six-month period (from 20-Feb 2024 to 20 August 2024) following the approval of the study synopsis. The sample size was determined using the WHO sample size calculator, ensuring a 95% confidence level and 80% study power. Based on the reported efficacy rates of SGLT-2 inhibitors (55.97%) and DPP-4 inhibitors (10.57%), the required sample size was calculated to be 46 patients (23 per group). However, following CPSP guidelines, the total sample size was increased to 60 patients, with 30 participants in each group. The study employed a non-probability consecutive sampling technique and the population selected with the condition to complete pre-defined inclusion/exclusion criteria. As the study is performed in general population, both genders were employed while the age was between 20-60 years. HbA1c level $\geq$7.0% in type 2 diabetics already taking ant hyperglycemic drugs with at least of 3 months. Furthermore, already with lower weight participants i.e. <22kg/m^2 BMI, type 1 diabetics, documented history of hypersensitivity with the trial drugs or those on glycemic management with insulin was the exclusion criteria.

Prior to study initiation, ethical approval was obtained from the Institutional Ethical Review Committee and CPSP. Informed consent was secured from all participants after explaining the study objectives and ensuring confidentiality of their data. Eligible patients were recruited from the Department of Medicine, and detailed medical histories, including clinical examinations, diabetes duration, family history, smoking habits, and hypertension status, were recorded. Participants were then randomly assigned to one of two groups through the lottery method. The first group was prescribed an SGLT-2 inhibitor (Empagliflozin 10 mg once daily) alongside their regular diabetic treatment, while the second group received a DPP-4 inhibitor (Sitagliptin 50 mg once daily) in addition to their usual diabetes regimen. Both groups were monitored over a 12-week period, with weight measurements taken at baseline and at the study's conclusion. Efficacy was defined as a weight reduction of more than 3% from baseline.

SPSS 25th version was used to perform various statistical tests including t test and chi square test to compare main outcome variable i.e. efficacy while other demographic variables were also computed and presented in graphical and tabulated form. The standard threshold of p value i.e. $\leq$0.05 was set to know the statistical difference.

RESULTS

Frequency Distribution of Demographic and Clinical Variables (n=60)

Regarding age distribution, most of the participants i.e. 53.3%(n=32) were between 20 to 40 years old, while the remaining 46.7%(n=28) were between 41 to 60 years of their age indicating a fairly representation of both age groups. Similarly, gender distribution shows not very higher difference in male and females by recorded 56.7%(n=34) compared to females 43.3%(n=26). We found not higher number of smokers i.e. 25.0%(n=15) and 75.0%(n=45) were non-smokers. When considering hypertension, approximately 41.7% of the participants had hypertension, whereas the remaining 58.3% did not have a history of hypertension suggesting a notable proportion of individuals in the study had existing cardiovascular (CVD) risk factors. Finally, the data on family history of obesity reveals that 45.0% of the participants had a family history of obesity, while 55.0% did not. This highlights that a significant portion of individuals had a genetic predisposition to obesity, which is a known risk factor for metabolic disorders.

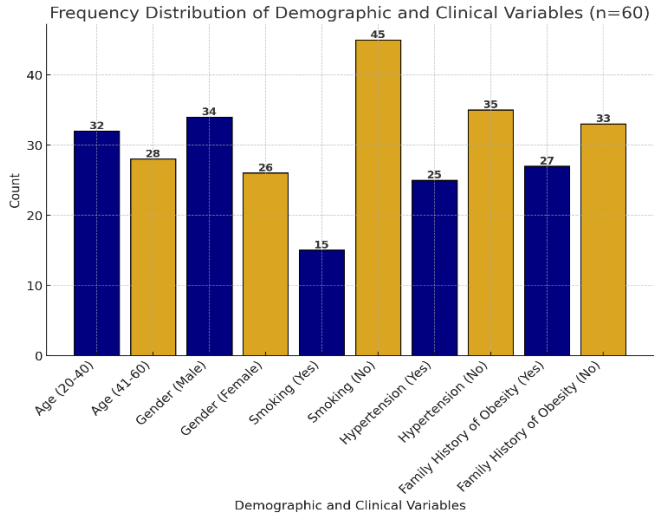
Table 1

Demographic and Clinical Profile(n=60)

Variable	Group	Count	Percent
Age(years)	20-40	32	53.3
	41-60	28	46.7
Gender	Male	34	56.7
	Female	26	43.3
Smoking	Yes	15	25.0
	No	45	75.0
Hypertension	Yes	25	41.7
	No	35	58.3
Family History of Obesity	Yes	27	45.0
	No	33	55.0

Figure 1

Graphical Presentation of Demographic and Clinical Variables



Description of Continuous Variables (n=60)

The dataset summarizes key continuous variables of a 60-participant cohort, reflecting their age, body composition, and diabetes duration. The mean age was 39.02 years (SD: 11.87), indicating a diverse age range. Participants had an average BMI of 27.86 kg/m² (SD: 3.43), placing many in the overweight category. The mean duration of diabetes was 8.84 years (SD: 3.99), demonstrating varying disease histories. The mean body weight was 87.93 kg (SD: 13.66), highlighting differences in body composition across individuals.

Table 2

Description of Continuous Variables(n=60)

Variable	Mean	N	Std. Deviation
Age	39.02	60	11.87
BMI	27.86	60	3.43
Duration of Diabetes	8.84	60	3.99
Body Weight	87.93	60	13.66

Comparison of SGLT and DPP Groups for Body Weight (n=60)

Table 3 compares the body weight, post-12-week weight, and percentage of weight reduction between the SGLT-2 inhibitor (SGLT) and DPP-4 inhibitor (DPP) groups using the independent t-test. The mean baseline body weight was comparable between the groups, with the SGLT group averaging 88.13 kg and the DPP group averaging 87.62 kg (p=0.89), indicating no significant difference at baseline. After 12 weeks of treatment, the post-treatment weight in the SGLT group decreased to 83.97 kg, whereas the DPP group showed a mean weight of 86.03 kg(p=0.56). The most significant difference was observed in the weight reduction percentage. Participants in the SGLT group experienced a significantly greater weight reduction (4.72% ± 0.74%) compared to those in the DPP group (1.78% ± 1.12%), with a highly significant p-value of 0.00.

Table 3

Comparison of SGLT and DPP Groups for Body Weight(n=60)

Variable	Group	N	Mean	Std. Deviation	P value*
Body Weight	SGLT	37	88.13	13.10	0.89
	DPP	23	87.62	14.80	
Post 12 Weeks Weight	SGLT	37	83.97	12.56	0.56
	DPP	23	86.03	14.36	
Weight Reduction %	SGLT	37	4.72	0.74	0.00
	DPP	23	1.78	1.12	

**Independent t test*

Comparison of Efficacy of SGLT and DPP Groups (n=60)

Table 4 evaluates the efficacy of both groups in achieving ≥3% weight reduction over 12 weeks. In the SGLT group, 88.1% (37 out of 37 participants) achieved the efficacy threshold, while in the DPP group, only 11.9% (5 out of 23 participants) achieved the same weight reduction. Conversely, all 18 participants (100%) in the DPP group who failed to achieve ≥3% weight reduction were classified as non-responders, whereas no non-responders were present in the SGLT group. A highly significant p-value of 0.00, further reinforcing that SGLT-2 inhibitors were markedly superior in promoting weight loss compared to DPP-4 inhibitors.

Table 4

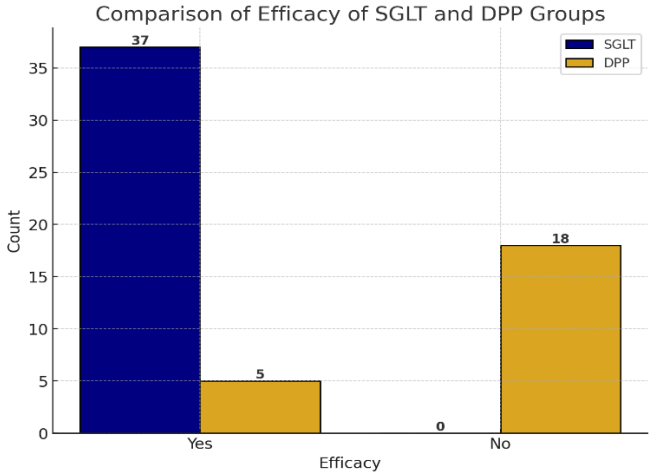
Comparison of Efficacy of SGLT and DPP Groups (n=60)

Efficacy	Groups		Total	P value*
	SGLT	DPP		
Yes	37 (88.1%)	5 (11.9%)	42 (100%)	0.00
No	0	18 (100%)	18 (100%)	

**Chi Square test*

Figure 2

Comparison of Efficacy in SGLT and DPP Groups



Comparison of Efficacy of SGLT and DPP Groups According to Various Effect Modifiers

Among participants aged 20–40 years, 92% (23/25) of those in the SGLT-2 group achieved at least a 3% weight reduction, compared to only 8% (2/25) in the DPP-4 group (p = 0.000). Conversely, all non-responders

(100%) in this age group were in the DPP-4 group. Similarly, in the 41–60 years age group, in the SGLT-2 group (82.4%) achieved the efficacy threshold, compared to only 17.6% in the DPP-4 group (p = 0.000). The trend across both age groups consistently shows better efficacy of SGLT-2 inhibitors in promoting weight loss compared to DPP-4 inhibitors.

Both males and females showed significant weight reduction with SGLT-2 inhibitors compared to DPP-4 inhibitors. Among male participants, 83.3% (20/24) in the SGLT-2 group achieved the target weight loss, compared to 16.7% (4/24) in the DPP-4 group (p = 0.000). Among females, 94.4% (17/18) in the SGLT-2 group met the weight reduction criterion, while only 5.6% (1/18) in the DPP-4 group achieved the same (p = 0.000). These results suggest that both genders benefit from SGLT-2 inhibitors, with a slightly greater efficacy observed in females.

The efficacy of SGLT-2 inhibitors was higher among both smokers and non-smokers. Among smokers, 81.8% (9/11) of SGLT-2 users achieved the target weight reduction, compared to 18.2% (2/11) in the DPP-4 group (p = 0.004). In non-smokers, the efficacy of SGLT-2 inhibitors was even higher (90.3% vs. 9.7%), with a highly significant p-value of 0.000. These findings suggest that smoking status does not impact the superior weight reduction efficacy of SGLT-2 inhibitors over DPP-4 inhibitors.

Among participants with hypertension, 78.6% (11/14) in the SGLT-2 group achieved the target weight reduction, whereas only 21.4% (3/14) in the DPP-4 group did so (p = 0.000). In non-hypertensive participants, the efficacy of SGLT-2 inhibitors was even greater (92.9%) compared to 7.1% in the DPP-4 group (p = 0.000). This suggests that SGLT-2 inhibitors are effective in reducing weight regardless of hypertensive status, but may be slightly more effective in non-hypertensive individuals.

Participants with a family history of obesity also showed significant weight reduction with SGLT-2 inhibitors. Among those with a positive family history, 80% (16/20) in the SGLT-2 group achieved the weight reduction, whereas only 20% (4/20) in the DPP-4 group did so (p = 0.000). In participants without a family history of obesity, 95.5% (21/22) in the SGLT-2 group achieved weight reduction, compared to 4.5% (1/22) in the DPP-4 group (p = 0.000). These findings suggest that SGLT-2 inhibitors provide substantial weight loss benefits regardless of genetic predisposition to obesity.

Table 5

Comparison of Efficacy of SGLT and DPP Groups According to Various Effect Modifiers (n=60)

Variable		Efficacy	Group-A (SGLT)	Group-B (DPP)	Total	P-value *
Age	20-40	Yes	23 (92%)	2 (8%)	25 (100%)	0.000
		No	0	7 (100%)	7 (100%)	
	41-60	Yes	14 (82. %)	3 (17.6%)	17 (100%)	0.000
		No	0	11 (100%)	11 (100%)	
Gender	Male	Yes	20 (83.3%)	4 (16.7%)	24 (100%)	0.000
		No	0	10 (100%)	10 (100%)	
	Female	Yes	17 (94.4%)	1 (5.6%)	18 (100%)	0.000
		No	0	8 (100%)	8 (100%)	
Smoking	Yes	Yes	9 (81.8%)	2 (18.2%)	11 (100%)	0.004
		No	0	4 (100%)	4 (100%)	
	No	Yes	28 (90.3%)	3 (9.7%)	31 (100%)	0.000
		No	0	14 (100%)	14 (100%)	
Hypertension	Yes	Yes	11 (78.6%)	3 (21.4%)	14 (100%)	0.000
		No	0	11 (100%)	11 (100%)	
	No	Yes	26 (92.9%)	2 (7.1%)	28 (100%)	0.000
		No	0	7 (100%)	7 (100%)	
Family History of Obesity	Yes	Yes	16 (80%)	4 (20%)	20 (100%)	0.000
		No	0	7 (100%)	7 (100%)	
	No	Yes	21 (95.5%)	1 (4.5%)	22 (100%)	0.000
		No	0	11 (100%)	11 (100%)	

**Chi Square test*

DISCUSSION

Managing weight is a challenging task in cases with T2DM due to direct influences of glycemic control and insulin resistance. Sodium-glucose cotransporter 2 (SGLT-2) and sodium-glucose cotransporter 2 (SGLT-2) inhibitors among the available anti hyperglycemic drugs reveal remarkable benefits for weight loss, whereas dipeptidyl peptidase-4 (DPP-4) inhibitors are associated with weight neutrality or minimal weight reduction. As we aimed to compare the efficacy of these two drug classes in reducing body weight among newly diagnosed T2DM patients over 12 weeks.

With regard to baseline characteristics, the age of our study participants was 39.02 years on average, with a marginally higher percentage of male participants (56.7%) than females (43.3%). Over half of the patients (53.3%) were between 20 to 40 years of age, while the others (46.7%) were between 41 to 60 years. Hypertension was observed in 41.7% of participants, and 25.0% of the cohort were smokers. A family history of obesity was present in 45.0% of cases.

Our demographic distribution aligns with the findings of Cheol Son et al.[12], who reported that Japanese T2DM patients receiving SGLT-2 inhibitors and DPP-4 inhibitors had a mean age of 55.3 years, with a male predominance. Similarly, Ildiko Lingvay et al.[13] studied a U.S. cohort with a higher mean age (57.2 years) and a higher prevalence of obesity compared to our study. In contrast, Pushkar Mani et al.[14] examined the Indian population and noted a younger diabetic cohort with higher BMI values, suggesting ethnic variations in metabolic risk profiles.

As for baseline characteristics, the mean age of our study population was 39.02 years, with a slightly higher proportion of male participants (56.7%) compared to female participants (43.3%). More than half of the patients (53.3%) were aged between 20 to 40 years, while the remaining (46.7%) were aged between 41 to 60 years. These findings are consistent with the Cantabile study by Cheol Son et al.[11], which demonstrated that 55.9% of patients in the SGLT-2 inhibitor group achieved ≥3% weight reduction, compared to only 10.5% in the DPP-4 inhibitor group. Similarly, Ayako Nagayama et al.[15] reported that SGLT-2 inhibitors resulted in an average weight reduction of 3.5 kg, whereas DPP-4 inhibitors led to only 1.1 kg weight loss, supporting our conclusion that SGLT-2 inhibitors have superior weight-lowering effects.

The weight reduction observed with SGLT-2 inhibitors is primarily attributed to their mechanism of action, which induces glycosuria and calorie loss, leading to a negative energy balance. Conversely, DPP-4 inhibitors act by enhancing incretin hormone activity, which improves insulin secretion without significantly affecting weight.

Moreover, Farazul Hoda et al.[16] confirmed that SGLT-2 inhibitors induce weight loss via caloric excretion through glycosuria, whereas DPP-4 inhibitors primarily improve postprandial insulin secretion without significantly impacting weight. In contrast, Paola Fioretto et al.[17] highlighted that DPP-4 inhibitors may provide modest weight loss when combined with metformin, but the effect is still inferior to SGLT-2 inhibitors.

Although SGLT-2 inhibitors have shown superior efficacy in weight reduction, their safety profile must also be taken into consideration. These drugs have been associated with an increased risk of urinary tract infections and ketoacidosis, whereas DPP-4 inhibitors have been linked to a higher incidence of heart failure in some studies. Our study did not assess adverse events, but future research should incorporate safety outcomes alongside efficacy measures to provide a more comprehensive evaluation of these drug classes.

CONCLUSION

Our study demonstrates that SGLT-2 inhibitors are significantly more effective than DPP-4 inhibitors in reducing body weight among newly diagnosed T2DM patients. Given the importance of weight management in diabetes care, SGLT-2 inhibitors may be the preferred option for patients requiring weight reduction as part of their treatment plan. Future studies with larger sample sizes and longer follow-up durations are warranted to further validate these findings and assess additional metabolic benefits.

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