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Original Article

Treatment Outcomes of Dipeptidyl Peptidase-4 Inhibitors and Sodium-Glucose Co-Transporter-2 Inhibitors in Diabetes Mellitus with Poor Glycemic Control

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Abstract

Background: *Diabetes, a progressive disease necessitating multifaceted pharmacological interventions for glycemic control, commonly employs Dipeptidyl Peptidase-4 inhibitors (DPP-4i) and Sodium-Glucose Co-Transporter-2 inhibitors (SGLT-2i). The ongoing challenge lies in determining the superior option for safety and efficacy.*

Objective: *This study aims to describe the treatment outcomes of DPP-4 inhibitors (DPP-4i) and Sodium-Glucose Co-Transporter-2 inhibitors (SGLT-2i) in individuals with diabetes mellitus (DM) receiving metformin with poor glycemic control.*

Methods: *This prospective study was conducted at the Endocrinology Outpatient Department of Dhaka Medical College Hospital, Dhaka, and included 90 individuals with diabetes mellitus who met the selection criteria. Divided into two groups, Group I (n=45) received DPP-4 inhibitors plus metformin, and Group II (n=45) received SGLT2 inhibitors plus metformin. Baseline data, including HbA1c, fasting blood glucose (FBG), blood glucose 2 hours after breakfast, weight, lipid profile, and serum creatinine, were recorded at the first visit and 12 weeks. Safety was assessed based on adverse drug effects.*

Results: *After 12 weeks, both groups exhibited significant reductions in HbA1c, FBG, and postprandial blood glucose levels. However, the SGLT-2i group demonstrated significant improvements in HbA1c (P<0.012), fasting plasma glucose (P<0.003), and postprandial glucose levels (P<0.001), along with a reduction in body weight (P<0.042). Hypoglycemia rates were low and balanced between groups. Notably, SGLT-2i usage correlated with an increased incidence of urinary tract infections (13.33% vs. 6.66% in DPP-4i) and exclusive genital infections (11.11%, P<0.022).*

Conclusion: *Diabetic patients receiving SGLT-2 inhibitors had better glycemic control and body weight improvements in comparison to DPP-4 inhibitors. However, SGLT-2 inhibitors encountered more genital infections than DPP-4 inhibitors.*

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Introduction

DPP-4 inhibitors are oral diabetes medications designed to impede the enzyme DPP-4[1]. DPP-4 is responsible for deactivating several incretins like GLP-1 and glucose-dependent insulinotropic polypeptide (GIP). Consequently, inhibiting DPP-4 could influence glucose regulation through multiple pathways[2].

All DPP-4 inhibitors exhibit similar efficacy in managing glycemia [3], leading to a modest improvement in glycated hemoglobin (A1C). They are compatible with most other diabetes medications[4,5] except for glucagon-like peptide 1 (GLP-1) receptor agonists, as combining them doesn't yield additional glucose-lowering effects.

In recent years, there has been a growing utilization of DPP4 inhibitors due to their weight-neutral nature and low risk of hypoglycemia[5]. Research conducted in older adults with type 2 diabetes has demonstrated the effectiveness and safety of DPP-4 inhibitors, showcasing minimal hypoglycemic events, no association with bone fracture risk, and a neutral stance regarding cardiovascular (CV) complications and mortality[6]. SGLT2 inhibitors function by enhancing the renal excretion of glucose, leading to a modest reduction in blood glucose levels among patients with type 2 diabetes. The osmotic diuresis induced by this therapeutic approach affects the heart, kidney, and other common metabolic pathways; hence, it is often associated with other comorbidities[7]. Managing multiple comorbidities in patients with T2DM may lead to polypharmacy. Drugs that can be given in various conditions are attractive to clinicians. One such drug class is SGLT-2 inhibitors, which can play a crucial role in reducing blood glucose levels, body weight, and blood pressure. Ultimately, it can reduce the risk of cardiovascular and renal outcomes without increasing hypoglycemic risk (8). SGLT-2 inhibitors are compatible with most other glucose-lowering agents[10] and can be used in patients with comorbid conditions, including atherosclerotic CVD, heart failure (HF), and chronic kidney disease (CKD)[10]. Indeed, choosing between SGLT2 inhibitors and DPP-4 inhibitors may be based on glucose-lowering efficacy and effects on body weight, tolerability, and cost[11]. DPP-4 inhibitors are commonly prescribed similarly to how SGLT2 inhibitors are prescribed for people with type 2 diabetes. Therefore, DPP-4 inhibitors are suitable active comparators to evaluate the effectiveness of SGLT2 inhibitors in adults with type 2 diabetes in the clinical setting[5]. Due to comorbidities and medications, Real-world patients are often diverse and complex. So, it is essential to recapitulate findings from clinical trials with real-world data. Clinicians often face challenges in selecting the most appropriate antidiabetic medication for patients with poor glycemic control. A head-to-head comparison of DPP-4 and SGLT-2 inhibitors will provide valuable data to guide evidence-based treatment decisions.

This study describes the therapeutic outcomes of DPP-4 and SGLT-2 inhibitors in uncontrolled type-2 diabetic patients receiving metformin. Outcomes were assessed by HbA1c, fasting blood sugar, blood sugar 2 hours after breakfast, changes in weight, lipid profile, and creatinine in different schedules (at baseline and 12 weeks after treatment). In addition, adverse effects like hypoglycemia, urinary tract infection (UTI), and genital infection developed in patients during this observation period were assessed as complications.

Methodology

Study Design:

This prospective study was conducted at the Department of Pharmacology and Therapeutics, Dhaka Medical College, Dhaka, From January 2021 to December 2021.

Objectives

General Objective

To describe the treatment outcomes of DPP-4 and SGLT-2 inhibitors in type 2 diabetes mellitus patients with poor glycemic control.

Specific Objectives:

To compare the reduction of the HbA1c, fasting, and 2 hours after breakfast blood glucose, body weight, GFR, and lipid profile among patients with uncontrolled diabetes mellitus starting DPP-4 inhibitors or SGLT-2 inhibitors along with previously started metformin at baseline and after 12 weeks of treatment

Describe each group's complications during the study period, such as hypoglycemia, UTI, and genital infection.

Study population:

The purposive sampling was taken from patients visited with Uncontrolled type 2 diabetic patients getting metformin aged from 18 years to 65 years to the Endocrinology Outpatient Department of Dhaka Medical College Hospital.

Study groups:

To determine the sample size for hypothesis testing, we used the following equation: $n = (z\alpha+z\beta)^2 \times \sigma1^2+\sigma2^2) / \mu1-\mu2)$. This was based on a previous study comparing the means of two groups - DPP4 inhibitors and SGLT2 inhibitors. The calculated sample size was 99, but we only had 90 participants due to time constraints. All the participants were then divided into their respective groups.

Group I: 45 patients treated with DPP4 inhibitors plus metformin for 12 consecutive weeks.

Group II: 45 patients treated with SGLT2 inhibitors plus metformin for 12 consecutive weeks.

Sample selection criteria:

Inclusion Criteria:

Patients with type 2 diabetes mellitus with poor glycemic control already treated with metformin.

Patients aged from 18 years to 65 years.

HbA1c ≥7%

GFR >60 ml/min.

Exclusion Criteria:

Type 1 Diabetes Mellitus

Gestational Diabetes Mellitus (GDM)

H/O Diabetic ketoacidosis within the last six months

H/O recurrent Urinary tract infection

GFR <60 ml/min.

Persistent elevation of serum transaminase level (more than three times the upper limit of normal)

Pancreatitis <6 months before enrollment.

Data collection procedure:

Patients were enrolled from the Endocrinology Outpatient Department (OPD) of Dhaka Medical College Hospital, Dhaka. The patients' demographics, past and present medication history, and other relevant data needed for the study were collected through face-to-face interviews and reviewing patients' prescriptions. Eligible patients with poor glycemic control, HbA1c e" 7.0%, with no contraindication to DPP-4 or SGLT-2 inhibitors were enrolled. And explained one of the DPP-4 inhibitors or SGLT-2 inhibitors) should be added on top of metformin. We explained the study procedure to outdoor physicians about the group of the study population and requested to prescribe one of the above medications. Respondents in whom DPP-4 inhibitors were added with metformin were in Group I, and SGLT-2 inhibitors were added with metformin in Group II but were not explored until the first follow-up. Baseline data of efficacy markers such as HbA1c, fasting blood glucose (FBG), blood glucose 2 hours after breakfast, weight, fasting lipid profile, and GFR were recorded in a data collection form during the first visit in both groups. About 50 patients were interviewed in each group, and their baseline data were recorded during the first visit.

Then, the patients were counseled for a follow-up visit after 12 weeks with their investigation reports and group number. During this time, they were requested to maintain their daily routine and diets. They were all given a chart that recorded any adverse consequences like hypoglycemia, allergic reactions, or vulval itching. We also provide an emergency contact number in case of severe adverse effects. In a follow-up visit, information on HbA1c, fasting blood glucose (FBG), blood glucose 2 hours after breakfast, weight, s. lipid profile, GFR, and any history of hypoglycemia, increased frequency of micturition, and vulval itching in the last 12 weeks were recorded in the data collection form in both groups. All completed data and lab reports were pooled together.

Ethical issues:

The study was done after the approval of the Ethical Review Committee (ERC) of Dhaka Medical College, Dhaka. Before this study, permission was also obtained from the Dhaka Medical College Hospital Authority. Informed written consent was taken from each respondent. They were assured that all information they provided would be confidential, and their name or anything that could identify them would not be published or exposed anywhere.

Data analysis:

All relevant information was collected, completed, and compiled. Collected data were analyzed by SPSS 26.0. Qualitative data were expressed as frequency distribution, and percentage and quantitative data were expressed as mean ± SD (standard deviation). Pair and an unpaired t-test was done for the means of two groups and the percentage of two samples' chi-square test. The p-value d" 0.05 was considered statistically significant at 95% CI (confidence interval).

Operational Definition:

Diabetes mellitus:

Any patient has diabetes who is diagnosed by any registered physician and with the following criteria of the American Diabetic Association (ADA). (13)

Fasting plasma glucose ≥126 mg/dl (7.0 mmol/L) or

2-hour plasma glucose after 75-g OGTT ≥200mg/dl (11.1mmol/L) or

HbA1c ≥6.5 % or

In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dl (11.1 mmol/L)

Complications: The safety of the drugs was assessed as to whether they produce side effects such as hypoglycemia, genital tract infection, or UTI.

HbA1c: Glycosylated hemoglobin is formed by non-enzymatic condensation of glucose with the globin component of hemoglobin. The rate of HbA1c formation is proportional to the ambient blood glucose concentration. HbA1c <5.7% is nondiabetic, 5.7-6.4% is prediabetes, and ≥6.5% is diabetes[14].

Hypoglycemia: When the blood glucose level is less than 3.9 mmol/L and is associated with clinical signs and symptoms such as sweating, hunger, anxiety, tachycardia, irritability, and confusion.

Genital tract infection is defined as an infection of the reproductive or genital tract that causes healthy life loss among sexually active women of reproductive age in

developing countries. A woman can represent various symptoms like backache, lower abdominal pain, vulval itching, and abnormal vaginal discharge. In men, it causes burning or itching in the penis, discharge from the penis, and pain when peeing[15].

Results

The patients were divided into two groups. In group I, 45 patients were treated with DPP-4 inhibitors plus metformin for 12 weeks and in group II, 45 patients were treated with SGLT-2 inhibitors plus metformin for 12 weeks. Demographic data and HbA1c, FBG, blood glucose 2 hours ABF, GFR, body weight, and lipid profile were measured at baseline and 12 weeks after treatment in both groups. Demographic characteristics and biochemical parameters were almost the same in both groups (Table 1 and 2).

Table 1. Demographic characteristics of the respondents

Characteristics	DPP4 group, n=45			SGLT-2 group, n=45			P
	N	%	Mean ± SD	N	%	Mean ± SD	value
Age							
20-29	2	4.44	46.7±9.12	1	2.22	48.5±7.9	0.06[a]
30-39	1	2.22		2	4.44		
40-49	26	57.77		23	51.11		
50-59	11	24.44		15	33.33		
60-65	5	11.11		4	8.88		
Sex							
Male	21	46.66		25	55.55		0.1[b]
Female	24	53.33		20	44.44		
Education							
Primary	2	4.44		1	2.22		0.59[b]
SSC	18	40		19	42.22		
HSC	14	31.11		12	26.66		
Graduate	9	20		10	22.22		
Post-graduate	2	4.44		3	6.66		
Profession							
Housewife	23	51.11		20	44.44		
Business	12	26.66		1	26.66		
Service	7	15.55		9	20		
Retired	3	6.66		3	8.88		
Duration of diabetes			5.86±2.6			6.24±3.28	
<5 years	25	55.55		27	60		0.068 [a]
5-10 years	16	35.55		14	31.11		
>10 years	4	8.88		4	8.88		
Family history of DM present	10	22.22		13	28.88		

Data were expressed as mean ± SD

a. An unpaired t-test was done to measure the level of significance.

b. Chi-square test was done to measure the level of significance.

$p < 0.05$ was considered significant throughout the study

Table 2. Comparison of basic biochemical and physical parameters at base line between the two study groups (n=90).

Characteristics	DPP4 group, n=45 Mean ± SD	SGLT-2 group, n=45 Mean ± SD	p value
HbA1c (%)	8.67 ± 1.78	8.15 ± 1.6	0.055
FBG	10.30±3.49	10.21±3.35	0.893
Blood glucose 2hrs ABF (mmol/L)	14.77±4.68	13.77±4.7	0.248
Mean body weight Kg	60.12±7.67	61.02±7.43	0.613
GFR (ml/min)	88.5 ±20.8	87.4± 22.7	0.214
Fasting lipid profile			
Cholesterol	188.0±41.8	203±39.1	0.08
Triglyceride	170.8±32.8	170.8±32.8	1.0
LDL-C	139.3±33.3	139.3±33.3	1.0
HDL-C	39.2±7.9	41.2±7.9	0.23

Data were expressed as mean±SD

Unpaired t-test was done to measure the level of significance.

$p < 0.05$ was considered significant throughout the study.

After 12 weeks of treatment all the parameters including fasting blood glucose, 2 hours after breakfast, and HbA1C all were significantly decreased in case of SGLT inhibitors but in case of lipid profile, and GFR reduction both group showed same efficacy, the mean fasting lipid profile level at baseline and 12 weeks after treatment in group I and group II which was not significantly changed in both groups. But considering all parameters of safety and efficacy SGLT is more efficacious than DPP4 inhibitors (Table 3 and 4).

Table 3. Comparison of biochemical and physical parameter in between two groups before and after treatment

Characteristics	DPP4 group, n=45			SGLT-2 group, n=45		
	At baseline Mean ± SD	After 12 weeks Mean ± SD	P value	At baseline Mean ± SD	After 12 weeks Mean ± SD	P value
Fasting blood glucose	10.30±3.49	8.88±3.55	0.001	10.21±3.35	7.21±2.31	0.001
HbA1c (%)	8.67 ± 1.78	7.70 ± 1.67	0.001	8.15 ± 1.6	7.05 ± 1.56	0.001
blood glucose 2hrs ABF	14.77±4.68	11.53±4.4	0.001	13.77±4.7	9.05±4.04	0.001
Fasting lipid profile mg/dl						
Cholesterol	188.0±41.8	189.2±39.9	0.560	203±39.1	204.4±42.4	0.073
Triglyceride	170.8±32.8	175.5±40.5	0.082	170.8±32.8	173.4±29.6	0.773
LDL-C	139.3±33.3	135.3±35.7	0.175	139.3±33.3	140.7±31.5	0.119
HDL-C	39.2±7.9	42.5±8.8	0.338	41.2±7.9	42.3±6.6	0.465
Body weight	60.12±7.67	60.35±6.40	0.563	61.02±7.43	57.89±7.25	<0.001
eGFR	88.5 ±20.8	90.9 ± 19.18	0.108	87.4± 22.7	89.6 ± 20.17	0.233

Data were expressed as mean±SD

Paired t-test was done to measure the level of significance.

$p < 0.05$ was considered significant throughout the study.

Table 4. Comparison of biochemical profile between two groups After 12 weeks of treatment

Characteristics	DPP4 group, n=45 After 12 weeks Mean ± SD	SGLT-2 group, n=45 After 12 weeks Mean ± SD	P value
Fasting blood glucose	8.88±3.55	7.21±2.31	0.003[b]
HbA1c (%)	7.70 ± 1.67	7.05 ± 1.56	0.012[b]
blood glucose 2hrs ABF	11.53±4.4	9.05±4.04	0.001[b]
Fasting lipid profile mg/dl			
Cholesterol	189.2±39.9	204.4±42.4	0.073
Triglyceride	175.5±40.5	173.4±29.6	0.428
LDL-C	135.3±35.7	140.7±31.5	0.126
HDL-C	42.5±8.8	42.3±6.6	0.223
Body weight	60.35±6.40	57.89±7.25	0.042[b]
eGFR	90.9 ± 19.18	89.6 ± 20.17	0.126[b]

Data were expressed as mean±SD and range.
unpaired t-test was done to measure the level of significance.

It was observed that patients had experienced hypoglycemia and Urinary tract infection in both groups in group but in case of genital infection SGLT group experienced more than DPP4 group and it was statistically significant (p = 0.022) (Table 5).

Table 5. Distribution of respondents by adverse effects (n=90)

Adverse Effects	DPP4 group, n=45		SGLT-2 group n=45		p - value
	n	%	n	%	
Hypoglycemia	6	13.3	8	17.7	0.311
UTI	3	6.66	6	13.33	0.298
Genital infection	0	0	5	11.11	0.022

Data were expressed as numbers and percentages.
A chi-square test was done to measure the level of significance.
p < 0.05 was considered significant throughout the study.

Discussion

The efficacy of a drug depends on various parameters, such as its therapeutic action, the inherent property of an agonist to elicit a physiological response when it binds with a receptor, and safety, mostly its side effects. Efficacy and safety are not a constant issue for every drug; they differ from drug to drug and the aim of the development of drugs. In the case of a hypoglycemic agent, efficacy is assessed by their blood glucose-lowering capacity, evaluated by HbA1c, FBG, blood glucose 2 hrs. after breakfast, and effect on body weight, GFR, and fasting lipid profile. The safety of the drugs was assessed as to whether they produce side effects such as hypoglycemia, genital tract infection, or urinary tract infection.

From the therapeutic points, both DPP-4 and SGLT2 inhibitors are prevalent drugs among physicians who manage diabetic patients for their excellent efficacy and safety profile. However, SGLT2 inhibitors with an insulin-independent mode of action might confer greater efficacy than DPP4 inhibitors with a partially insulin-dependent mode.

This study showed a significant reduction of FBG in both study groups after 12 weeks of treatment, but there was a substantial difference between the two groups (p=0.003). This result is also like other studies done[16]. After 12 weeks of treatment, HbA1c was significantly reduced by SGLT inhibitors more than DPP4 inhibitors. On comparison between the two groups, it was statistically significant (p=0.012). One study also found similar results[17].

Maintaining body weight is an essential factor in case diabetes management. Increased body weight is associated with insulin resistance, lowering the oral hypoglycemic agent's efficacy. After 12 weeks of treatment, group II had significant body weight reduction. The change in mean body weight was statistically significant between study groups (p<0.042). The potential for reduction in body weight is a notable feature of SGLT2 inhibitors[18,19,20]. It may make them valuable agents to combine with other antidiabetic therapies to reduce glucose levels further and facilitate weight loss or mitigate any weight gain associated with improved glycemic

control[20]. Caloric loss through urinary glucose excretion may be an essential contributor to this effect[22].

Effects on GFR: both drugs showed similar efficacy. GFR was raised after 12 weeks in both groups, but it was insignificant. The comparison between the two groups was not statistically significant (p=0.777). One study found a similar result[22]. DPP-4 inhibitors have no effect on creatinine, and SGLT-2 inhibitors have a renoprotective impact but on GFR; no significant effect found might be due to the short duration of the study period[23].

There was little change in the fasting lipid profile after 12 weeks among the same group and between the two groups, which was also not statistically significant in the same group and between the two groups. This result is consistent with studies done in Taiwan[23]. There was a small sample size, and the three-month study period was insufficient to change the lipid profile[23].

In this study, Respondents experienced slightly more hypoglycemia when treated with SGLT-2 inhibitors than with DPP-4 inhibitors. However, the incidence of hypoglycemia was almost similar in both groups. In comparison between the two groups, there was statistically no significant difference (p = 0.311). The result was identical to previous trials[24,25,26]. The possible mechanism behind the lower hypoglycemic rate with linagliptin and empagliflozin may be related to the glucose-dependent enhancement of insulin secretion and greater a-cell sensitivity of DPP-4 inhibitors to hypoglycemia (27,28) and glucose-independent mechanism of action.

In this study, respondents treated with SGLT-2 inhibitors developed more UTIs than with DPP-4 inhibitors (6.66% and 13.33%, respectively). In comparison between the two groups, there was statistically no significant difference (p = 0.298). This study about UTIs is like various studies that show UTIs at 4% in SGLT-2 inhibitors and 4 % in the DPP-4 inhibitors group. The pharmacologically induced urinary glucose with SGLT-2 inhibitors may cause additional growth of commensal microorganisms[28].

There were genital infections in the SGLT-2 inhibitors group (11.11%) but not in this study's DPP-4 inhibitors group, which was statistically significant (p = 0.022). The result is consistent with one study(8), which showed more frequent genital infections in SGLT-2 inhibitor users (p<0.001). SGLT-2 inhibitors cause glycosuria, making the genital area more conducive to bacterial infections[28].

Limitations:

Small sample size, short duration, purposive sampling, lost to follow up, and single center were the limitations of this study.

Conclusion

Diabetic patients receiving SGLT-2 inhibitors had better glycemic control and body weight improvements compared to DPP-4 inhibitors. However, SGLT-2 inhibitors encountered more urinary tract infection than DPP-4 inhibitors. So, physicians must be concern about genital tract infections while prescribing SGLT-2 inhibitors.

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