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Original Article

Efficacy And Safety Of Sodium-Glucose Cotransporter-2 (Sglt2) And Dipeptidyl Peptidase-4 (DPP-4) Inhibitor Combination Therapy In Patients With Type 2 Diabetes Inadequately Controlled By Metformin

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ABSTRACT

Objective: To evaluate the effectiveness and safety of combining SGLT2 inhibitors with or without DPP4 inhibitors as an add-on therapy for type 2 diabetes patients.

Study Design: Quasi-Experimental Study

Place and Duration of Study: Dr. Ruth KM Pfau Civil Hospital and Dow University Hospital Ojha Campus, Dow University of Health Sciences, Karachi, Pakistan, from Mar 21 to Dec 23.

Methodology: The study assessed type 2 diabetes patients on Metformin alone with an HbA1c level exceeding 7% and evaluated various clinical and biochemical markers.

Results: In a study of 239 obese and poorly controlled diabetic patients, 58.58% were female, and 41.42% were male, with an age range of 40-60 years. Diabetes duration was below 5 years in 17.57% of patients, between 5 and 10 years in 44.45%, and over 10 years in 38.07%. The treatment groups were as follows: Metformin + SGLT2 inhibitors (27.00%), Metformin + DPP4 inhibitors (32.00%), and all three combinations (41.00%). During a span of 36 weeks, a significant difference was seen in the levels of HbA1c ($p < 0.001$). Moreover, the BMI of male subjects. In addition, there were significant decreases in FBS, RBS, and triglyceride levels, whereas creatinine levels did not change.

Conclusion: Metformin, when combined with SGLT2 and DPP4 inhibitors, improves glycaemic control and weight reduction in morbid obesity patients, especially in males, with significant changes in HbA1c, fasting, and postprandial glucose levels.

Keywords: DPP4 Inhibitors; Glycaemic Control; Lipid Profiles; Metformin; Renal Function; SGLT2 Inhibitors; Type 2 Diabetes.

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INTRODUCTION

Untreated type 2 diabetes may result in chronic complications such as cardiovascular, cerebrovascular, and retinal changes, eventually causing ischaemic heart disease, stroke, blindness, and nephropathy, respectively.[1] The main cause of diabetes is an unbalanced diet as well as lifestyle.[2] If diet and exercise are not enough, a medicine called Metformin is usually prescribed as the first choice. Three of the most recent oral hypoglycaemics with fewer side effects are dipeptidyl peptidase 4 (DPP4) and sodium-glucose cotransporter 2 (SGLT2) inhibitors.[3,4] Metformin is certainly safer and more efficacious compared to sulfonylureas as a treatment for diabetes mellitus (DM), helping in reducing weight and even beneficial for cardiovascular mortality.[5] In RCTs and routine care, combination therapy with Metformin and a DPP4 inhibitor safely exerts good glycaemic control with fewer significant adverse events than other oral hypoglycemic drugs.[6] SGLT2 inhibitors are more effective than DPP4 inhibitors for controlling weight loss, fasting plasma glucose, and HbA1C and are weight neutral.[7] The combined use of SGLT2 and DPP4 inhibitors has been demonstrated to dramatically lower HbA1C levels.[8]

Compared to insulin, DPP4 inhibitors provide a decreased risk of hypoglycemia when used as a triple add-on therapy in patients with uncontrolled diabetes.[9] In comparison to dual Metformin and SGLT2/DPP4 inhibitors, SGLT2 and DPP4 inhibitors in combination with Metformin exhibit superior efficacy in Asians in terms of glycaemic control. Sushrima et al., comprehensive analysis revealed that, in contrast to white populations, Asian populations showed encouraging glucose-lowering effects from SGLT2 and DPP4 inhibitors.[10]

The purpose of this research is to examine glycaemic control, hypoglycemic episodes, renal dysfunction, and weight loss in type 2 diabetes

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patients who have not maintained acceptable glycaemic control on Metformin alone. The combination of SGLT2 and DPP4 inhibitors has been studied as a successful add-on treatment. Our objective in evaluating these characteristics is to provide vital information on the safety and efficacy of this combination therapy for treating type 2 diabetes.

METHODOLOGY

The study was carried out at Dr. Ruth KM Pfau Civil Hospital and the Dow University Hospital Ojha Campus of DUHS, Karachi, Pakistan, from Mar 21 to Dec 23. Ethical approval was obtained from the Ethics Committee of Dow University of Health Sciences, with reference number IRB-2344/DUHS/approved/2021/690.

Inclusion Criteria: Patients with Metformin monotherapy-treated type 2 diabetes mellitus between the ages of 18 and 70, of either gender, with HbA1C values of > 7% and a minimum of 1 to 10 years of diabetes duration were included in the study.

Exclusion Criteria: Patients on oral hypoglycemic medications, type 1 or gestational diabetes, renal failure, and chronic liver disease were among the exclusion criteria.

A sample of 10,000 patients screened for inclusion into the Type-2 diabetic patient database maintained at Dr. Ruth KM Pfau Civil Hospital and Dow University Hospital Ojha Campus in Karachi was obtained. We determined the optimal study size (n) required for representability based on that population by using typical random sampling methods. It leads to a decision where we choose n = 218 as our sample size. The ratio of 1:4 was maintained, and ranked sample sizes (N/n) were chosen where systematic sampling with a constant interval, k = N/n, would be achieved. We intended to collect the information by implementing a constant sampling interval (k = N/n); k≈46 ≈ n, guaranteeing that only 1 out of every 46 participants in the population were selected. A random starting point was chosen, and subsequently, every fourth patient was selected from the list of eligible candidates.

To compare the efficacy of Metformin in combination with SGLT2 inhibitors and DPP4 inhibitors in diabetics with inadequate glycaemic control. The sample size was determined utilizing the WHO sample size calculator, incorporating a confidence interval of 95% and a margin of error of 5%. The prevalence of diabetes mellitus (DM) among the adult population in Pakistan is reported to be 17.1%, as indicated by the IDF Diabetes Atlas 9th Edition. With a prevalence ratio of 17 per 1000 and a prevalence difference ranging from 12 to 22, a sample size of 218 is sufficient to achieve 80% power for detecting a 95% confidence interval and an odds ratio of 4. Based on these results, the population proportion under the null hypothesis (P0) is established at 0.5. The initial target of 70 patients per group was revised to 85 patients, considering expected withdrawal rates. The trial focused on 239 individuals out of a total of 300. Of the participants, forty percent took both SGLT2 and Metformin DPP4 inhibitors, and the remaining twenty-seven percent took both Metformin and SGLT2 inhibitors.

HbA1C, lipid profile, random blood sugar (RBS), serum creatinine, urine microalbumin levels, and fasting blood glucose (FBG) were the tests that made up the baseline. The demographic data, medical history, and findings of the clinical examination were gathered using a standardised pro forma. Participants also had to record their blood glucose levels and report hypoglycemic events during the follow-up tests, which were administered at 12–18 weeks. 19–24 weeks and 25–36 weeks. Participants received education on managing their diabetes, including changes to diet and lifestyle such as regular exercise. To evaluate changes in glycaemic control and secondary outcomes like weight, lipid profile, renal function, and hypoglycemic episodes.

Data was analyzed by using Statistical Package for Social Sciences (SPSS) 22.00. Quantitative data was represented using mean ± standard deviation and qualitative data was represented by using percentage and frequency. ANOVA test was applied and p-value of ≤ 0.05 was considered as statistically significant

RESULTS

The study involved 239 patients, aged 40–60 years, including 140 women and 99 men. Among the three treatment groups, 27% of patients were treated with Metformin inhibitors and SGLT2, 32% with DPP4 inhibitors, and 40% with a regimen of Metformin, DPP4 inhibitors, and SGLT2 inhibitors (Figure-1).

The participants were moderately obese with an average BMI of 28–30 kg/m² and exhibited uncontrolled diabetes, as evidenced by elevated levels of HbA1c, fasting blood glucose, and random blood glucose. Abnormal urinary microalbumin levels were observed, and dyslipidaemia was evident, characterised by increased triglycerides, low-density

lipoprotein (LDL), and total cholesterol levels (Table-I).

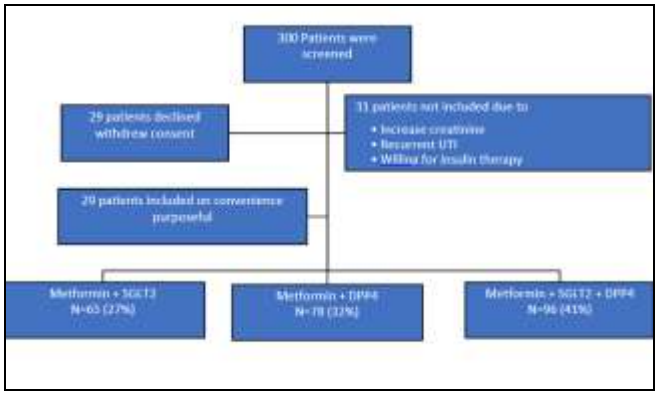

Figure-1: Enrolment of Patients

During the nine-month follow-up, significant enhancements were noted in BMI, HbA1c, FBS, RBS, and lipid profiles across all treatment groups. BMI showed a reduction of 2.6% to 5.4%, while HbA1c levels decreased by 13.2% to 21.6%. The reductions in FBS and RBS ranged from 24.1% to 35.3%. Men undergoing triple therapy experienced more substantial improvements in HbA1c and FBS, while women in the SGLT2 group exhibited greater reductions in BMI.

Urinary microalbumin levels significantly decreased from 53.7% to 66.3%, and serum creatinine levels remained stable across all groups. Improvements in the lipid profile included reductions in total and LDL cholesterol by 31.4% and 32.1%, respectively, and an increase in high-density lipoprotein (HDL) from 11.4% to 26.7%. Neutral fat levels decreased from 28.2% to 42.3% (Table-II).

DISCUSSION

The study investigated the efficacy and safety of dual combination therapy of Metformin with either DPP4 inhibitors or SGLT2 inhibitors, or triple combination therapy of Metformin with DPP4 inhibitors and SGLT2 inhibitors in type 2 diabetes mellitus patients poorly controlled on Metformin monotherapy. Efficacy was assessed to achieve HbA1c of less than 7%, FBS of less than 120 mg/dl, and RBS of less than 170 mg/dl. In addition, renal safety was monitored by urinary microalbumin and serum creatinine, and changes in the lipid profile were also assessed. Safety was assessed during the study period by documentation of hypoglycemic events by the patients during home monitoring, along with any side effects of medications, and regular monitoring of renal functions during follow-up. Most of the patients were in the age group between 40 and 60, with female dominance. Regarding the duration of diabetes, a considerable number of patients had it for more than five years, and a larger proportion had it for more than 10 years. Patients had different comorbid conditions like hypertension, obesity, ischaemic heart disease, dyslipidaemia, chronic airway disease, and cardiovascular disease, along with uncontrolled diabetes. These comorbid conditions must be controlled along with glycaemic control to prevent morbidity and mortality in diabetes patients.[11] Maintaining HbA1c at or less than 7% and blood pressure below or equal to or less than 130/80 mmHg can decrease both microvascular and macrovascular complications in type 2 diabetes patients.[12]

Table-I: Three Treatment Groups were Employed to Evaluate Every Variable (n=239)

Variables	Gender	DPP4+Met (OADs) n=65 (27%)	SGLT2 + Met (OADs) n=78 (32%)	DPP4+SGLT2+Met (OADs) n=96 (41%)	*p*-value
Age (years)	Male	50.81±10.00	38.71±70.00	52.7±10.00	0.01
	Female	45.19±15.00	44.75 ±20.00	45.48±15.00	0.49
BMI (kg/m²)	Male	28.62±2.38	29.04±3.11	29.18±2.55	0.61
	Female	28.67±3.61	30.33±2.55	29.50±2.64	0.03
HbA1C (%)	Male	8.53±0.67	8.03±0.63	8.98±0.89	<0.001
	Female	8.24±0.61	8.82±0.90	9.06±0.82	<0.001
FBS (mg/dl)	Male	162.28±28.58	155.08±26.32	177.33±37.45	0.01
	Female	166.09±25.88	165.95±27.66	171.61±34.37	0.56
RBS (mg/dl)	Male	228.60±22.29	231.62±42.01	248.02±33.91	0.02
	Female	232.06±33.35	244.21±40.97	255.35±35.82	0.00
UMA (mg/dl)	Male	52.42±0.94	84.95±76.29	69.60±63.05	0.15
	Female	64.51±54.22	89.39±74.90	68.97±78.70	0.22
Serum Creatinine (mg/dl)	Male	0.94±.21.00	0.87±.91.00	0.94±.21.00	0.42
	Female	0.85±.20.00	0.96±.22.00	0.95±.25.00	0.05
Total cholesterol (mg/dl)	Male	187.03±31.60	193.33±52.03	215.76±38.25	0.001
	Female	180.15±31.20	204.70±38.25	207.16±38.02	<0.001
HDL (mg/dl)	Male	38.81±7.81	34.70±7.18	35.14±9.90	0.12
	Female	35.42±7.00	33.39±6.33	35.55±1.05	0.38
LDL (mg/dl)	Male	134.03±33.12	125.37±42.86	143.16±34.92	0.15
	Female	119.31±26.84	121.39±43.37	127.68±46.68	0.55
Triglyceride (mg/dl)	Male	200.03±59.80	222.41±99.41	248.93±103.58	0.06
	Female	182.66±57.24	241.56±79.50	235.25±100.91	0.001

Table-II: Outcomes and Changes Among Treatment Groups from Baseline to 36 weeks

Variables	Gender	Treatment groups	Baseline	12-18 weeks	19-24 weeks	25-36 weeks	*p*-value
BMI Kg/m2	Male n=99	Met + SGLT2 (OADs) n=24	29.04±3.11	28.75 ±3.17	28.58±3.12	28.37±3.04	<0.001
		Met+ DPP4(OADs) n=33	28.62±2.38	28.25 ± 2.35	28.05±2.30	28.07±2.30	<0.001
		Met+ SGLT2+DPP4(OADs) n=42	29.18±2.55	28.78 ±2.50	28.66±2.66	28.12±2.66	< 0.001
	Female n=140	Met + SGLT2 (OADs) n=41	30.33±2.55	29.95±2.56	29.93±2.65	29.52±2.53	<0.001
		Met+ DPP4 (OADs)n=45	28.67±3.61	28.65±3.08	28.56±3.01	28.42±2.97	<0.001
		Met + SGLT2 + DPP4 (OADs) n=54	29.50±2.64	28.90±2.61	28.61±2.80	28.28±2.57	<0.001
HbA1c %	Male	Met + SGLT2 (OADs) n=24	8.03±0.63	7.25±0.59	7.06±0.44	6.77±0.42	<0.001
		Met + DPP4 (OADs) n=33	8.53±0.67	7.65±0.60	7.56±0.61	7.40±0.58	<0.001
		Met+ SGLT2+DPP4 (OADs) n=42	8.98±0.89	7.94±0.75	7.75±0.75	7.20±0.66	<0.001
	Female	Met+ SGLT2 (OADs) n=41	8.82±0.90	7.71±0.65	7.62±0.70	7.26±0.60	<0.001
		Met+ DPP4 (OADs) n=45	8.24±0.61	7.44±0.67	7.37±0.61	7.16±0.55	<0.001
		Met+ SGLT2+DPP4 (OADs) n=54	9.06±0.82	7.91±0.70	7.71±0.73	7.11±0.67	<0.001
FBS mg/dl	Male	Met+ SGLT2 (OADs) n=24	155.08±26.32	121.79±17.4	119.58±14.02	112.25±9.81	<0.001
		Met+ DPP4 (OADs) n=33	162±28.58	121.81±11.9	120.39±9.89	116.33±8.14	<0.001
		Met+ SGLT2+DPP4 (OADs) n=42	177.33±37.45	130.07±24.14	124.45±9.06	115.14±6.04	<0.001
	Female	Met+ SGLT2 (OADs) n=41	165.95±27.66	129.95±13.75	127.39±14.13	117.43±9.51	<0.001
		Met+ DPP4 (OADs) n=45	166.09±25.88	121.84±12.48	120.44±13.31	116.20±9.87	<0.001
		Met+ SGLT2+DPP4 (OADs) n=54	171.61±34.37	127.61±14.10	124.94±12.73	114.57±8.38	<0.001
RBS mg/dl	Male	Met+ SGLT2 (OADs) n=24	231.62±42.01	181.62±30.24	173.33±18.6	161.41±11.07	<0.001
		Met+ DPP4 (OADs) n=33	228.60±22.29	185.78±22.97	181.72±16.90	173.18±18.41	<0.001
		Met+ SGLT2+DPP4 (OADs) n=42	248.02±33.91	188.30±25.45	186.40±17.13	168.21±13.54	<0.001
	Female	Met+ SGLT2 (OADs) n=41	244.21±40.97	192.14±28.90	189.51±28.62	172.00±16.84	<0.001
		Met+ DPP4 (OADs) n=45	232.06±33.35	185.15±28.11	181.73±21.20	168.46±18.76	<0.001
		Met + SGLT2+DPP4 (OADs) n=54	255.35±35.82	186.96±26.89	181.31±19.96	165.27±13.82	<0.001
UMA mg/d	Male	Met+ SGLT2 (OADs) n=24	84.95±76.29	47.91±48.54	34.95±33.03	30.41±26.16	<0.001
		Met+ DPP4 (OADs) n=33	52.42±50.94	35.21±37.57	26.12±18.85	24.30±15.00	<0.001
		Met+ SGLT2+DPP4 (OADs) n=42	69.60±63.05	35.02±43.94	28.57±27.39	23.90±12.30	<0.001
	Female	Met + SGLT2 (OADs) n=41	89.39±74.90	36.82±30.59	33.90±24.59	30.26±17.78	<0.001
		Met+ DPP4 (OADs) n=45	64.51±54.22	35.84±36.35	30.00±21.84	27.62±14.37	<0.001
		Met+ SGLT2+DPP4 (OADs) n=54	68.97±78.70	35.16±41.60	28.31±17.74	23.94±11.84	<0.001
Serum creatinine mg/dl	Male	Met+ SGLT2 (OADs) n=24	0.87±0.91	0.87±0.17	0.92±0.17	0.92±0.17	0.169

Diabetes with obesity is a great challenge for the treating physician, as these patients are more likely to have long-term systemic complications.[13] Metformin and SGLT2 inhibitors, either used together or

		Met+ SGLT2+DPP4 (OADs) n=42	0.94±.21	0.93±0.19	0.96±0.20	0.96±0.20	0.169
	Female	Met+ SGLT2 (OADs) n=41	0.96±.22	0.94±0.16	0.93±0.15	0.93±0.15	0.907
		Met+ DPP4 (OADs) n=45	0.85±.20	0.90±0.18	0.91±0.18	0.91±0.18	0.907
		Met+ SGLT2+DPP4 (OADs) n=54	0.95±.25	0.94±0.22	0.93±0.21	0.93±0.21	0.907
Total cholesterol mg/dl	Male	Met+ SGLT2 (OADs) n=24	193.33±52.03	168.08±43.63	152.33±19.05	175.45±129.75	<0.001
		Met+ DPP4(OADs) n=33	187.03±31.60	158.78±18.45	152.63±14.07	151.15±13.06	<0.001
		Met+ SGLT2+DPP4 (OADs) n=42	215.76±38.25	159.14±24.29	152.60±20.27	148.48±17.86	<0.001
	Female	Met+ SGLT2 (OADs) n=41	204.70±38.25	159.14±24.29	152.60±20.27	148.48±17.86	<0.001
		Met + DPP4 (OADs) n=45	180.15±31.20	150.68±28.25	144.48±20.15	142.68±18.98	<0.001
		Met+ SGLT2+DPP4 (OADs) n=54	207.16±38.02	159.61±39.38	147.22±23.23	142.01±23.85	<0.001
HDL mg/dl	Male	Met+ SGLT2 (OADs) n=24	34.70±7.18	39.08±5.56	40.62±4.17	41.79±4.41	<0.001
		Met + DPP4 (OADs) n=33	38.81±7.81	41.06±6.71	40.81±6.81	43.24±16.77	<0.001
		Met+ SGLT2+DPP4 (OADs) n=42	35.14±9.90	41.57±7.94	42.66±7.10	44.54±6.06	<0.001
	Female	Met+ SGLT2 (OADs) n=41	33.39±6.63	39.46±5.22	40.12±4.57	41.36±4.31	<0.001
		Met+ DPP4(OADs) n=45	35.42±7.00	39.46±5.22	39.35±5.02	40.48±4.77	<0.001
		Met+ SGLT2+DPP4 (OADs) n=54	35.55±10.05	40.48±8.20	41.51±7.63	43.42±7.11	<0.001
LDL mg/dl	Male	Met+ SGLT2 (OADs) n=24	125.37±42.86	104.25±35.75	95.29±20.7	95.16±19.87	<0.001
		Met+ DPP4 (OADs) n=33	134.03±33.12	101.96±16.46	100.09±14.39	101.57±13.63	<0.001
		Met+ SGLT2+DPP4 (OADs) n=42	143.16±34.92	102.61±21.49	99.48±16.24	97.09±18.81	<0.001
	Female	Met+ SGLT2 (OADs) n=41	121.39±43.37	102.43±20.27	100.36±16.52	99.80±15.60	<0.001
		Met+ DPP4 (OADs) n=45	119.31±26.84	102.97±22.02	98.86±14.42	99.68±13.67	<0.001
		Met+ SGLT2+DPP4 (OADs) n=54	127.68±46.68	102.16±30.28	95.59±21.72	96.75±18.73	<0.001
Triglyceride mg/dl	Male	Met+ SGLT2 (OADs) n=24	222.41±99.41	180.04±83.11	153.37±34.81	146.66±29.07	<0.001
		Met+ DPP4 (OADs) n=33	200.03±59.80	159.27±45.79	152.81±37.02	143.57±38.74	<0.001
		Met+ SGLT2+DPP4 (OADs) n=42	248.93±103.58	161.47±47.56	151.02±35.65	143.57±28.35	<0.001
	Female	Met+ SGLT2 (OADs) n=41	241.56±79.50	175.14±45.96	164.51±33.72	155.36±26.68	<0.001
		Met+ DPP4 (OADs) n=45	182.66±57.24	150.66±43.76	143.31±31.32	137.31±32.76	<0.001
		Met+ SGLT2+DPP4 (OADs) n=54	235.25±100.91	169.94±71.40	152.42±35.22	145.07±31.55	<0.001

Repeated measures ANOVA for analysis. Mean difference is significant at 0.05 level.

separately, have been found to reduce weight, whereas DPP4 inhibitors, when used alone, are weight-neutral, but in combination with Metformin, they decrease BMI.[14] In our study, all the patients included were obese and had uncontrolled diabetes on Metformin monotherapy. These patients, when subjected to a dual or triple combination of medications, showed a significant degree of reduction in BMI over a period of 36 weeks, with no difference in the degree of BMI reduction in males in all three groups. However, BMI reduction was more profound in females on combination therapy with SGLT2 inhibitors. This may be because of the alteration of visceral fat adipokines, which control metabolic

activities, resulting in a decrease in BMI, as reported in a study by Bashier *et al*.[15]

All the patients in the three groups had their FBS and RBS checked at three intervals: firstly, after 12 to 18 weeks, then at 19 to 24 weeks, and at 25 to 36 weeks' intervals. In all three groups, patients showed a gradual decline in both FBS and RBS, and the mean FBS of 105 mg/dl to 120 mg/dl and mean RBS of 160 mg/dl to 180 mg/dl were achieved. The results were statistically significant in all the groups, but the triple combination group in males showed a greater decline in both FBS and RBS.16 On the other hand, in females, there was no difference in the decline of both FBS and RBS across the three treatment groups. Similar results were reported by Hsia et al., in a systematic review and meta-analysis.[16]

Although a few hypoglycemic events were reported by the patients on both dual combinations with SGLT2 inhibitors and the triple combination group during home monitoring, by adjusting the dose, these events were taken care of. Xu *et al.*,discussed the safety of triple combination therapy regarding hypoglycemic events.[17] So with the addition of SGLT-2 inhibitors, good glycaemic control can be achieved. This may be because of the varied mechanisms of action of these medications working together to achieve glycaemic control. Similarly, HbA1C showed a significant decline in all three groups during the study period, with a greater decline in combination groups on SGLT2 inhibitors.[17] This may be due to the distinctive mechanism of action of this group of medications, which is independent of insulin. The main mechanism is excreting glucose in urine by inhibiting the reabsorption of glucose in proximal renal tubules and thus decreasing glucotoxicity, improving beta cell function, and increasing insulin resistance rather than increasing insulin release.[18] Further benefits of SGLT2 inhibitors in improving renal profiles in diabetic patients are no doubt a distinct action of these medications by improving glomerular function and thus decreasing proteinuria; this has been assessed in different studies. It reduces intraglomerular pressure, improves tubular oxygenation and metabolism, and reduces renal inflammation and fibrosis. In our study, renal function was determined by checking urine for microalbumin and serum creatinine during each follow-up. Although all the subjects had urine microalbumin levels in the abnormal range at the start of the study, a significant decline was observed during the treatment period in all three groups. Serum creatinine was normal at the start of treatment and remained normal, showing no deterioration in renal function in all three groups, like the findings of the study by Lin *et al*.[19]

There is an increased frequency of dyslipidaemia in diabetic patients, thus increasing the risk of cardiovascular disease, peripheral vascular disease, and stroke. Regular monitoring and treatment for dyslipidaemia can prevent these comorbid conditions, so management of diabetes is not only glycaemic control but rather a multitasking state. All our patients had increased total cholesterol, LDL, and triglycerides at the start. They were advised dietary restrictions for lipids and 20 minutes of brisk walking daily. Over a period of 36 weeks' treatment, there was a significant decline in all these serum levels in all treatment groups. In addition, serum HDL also showed improvement in all the patients. Metformin alone has been shown to improve lipids in statin-naive patients by improving insulin sensitivity, weight reduction, and decreasing irreversibly glycated LDL-C levels. These levels were also reported by Rameshrad et al. 20 DPP4 inhibitors improve the lipid profile by reducing lipid absorption and synthesis and increasing lipid exertion. On the other hand, Szckeres *et al.,* described that SGLT2 inhibitors improve the lipid profile more uniquely by decreasing lipid accumulation in visceral fat, regulating serum lipoprotein levels, reducing lipid oxidation, and affecting oxidation and transportation of lipid molecules in the cells, resulting in changes in lipid metabolism and thus preventing an increase in LDL.[21]

So, giving a combination of different oral hypoglycaemic medications with different mechanisms of action to control the glycaemic levels has shown additional benefits of weight reduction and maintaining and improving renal and lipid profiles. Long-term follow-up of these patients is required to study other systemic outcomes in terms of cardiovascular, retinal, and cerebrovascular benefits.

LIMITATION OF STUDY

The limitation of this study is that the dose and different compounds of both DPP4 inhibitors and SGLT2 inhibitors used in the patients are not specified. Although, for achieving the targeted HbA1c, the dose of these medications was built up on follow-up as required, taking care of hypoglycemic events at the same time.

CONCLUSION

Metformin, when combined with SGLT2 and DPP4 inhibitors, improves glycaemic control and weight reduction in morbid obesity patients, especially in males, with

significant changes in HbA1c, fasting, and postprandial glucose levels. The study concluded that intensifying therapy with and without DPP4 and SGLT2 inhibitors in patients with uncontrolled diabetes on Metformin monotherapy is mostly tolerable. In addition, it has shown benefit in not only achieving the targeted HbA1c level but also in improving renal function and controlling dyslipidemia. The addition of SGLT2 inhibitors has, no doubt, shown a much better outcome in our patients. So, the combination of different groups of oral hypoglycemic agents can be a good choice, particularly for patients reluctant to shift to insulin therapy.

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Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

DK & SB: Data acquisition, data analysis, critical review, approval of the final version to be published.

SMK & PK: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

REFERENCES

1. Kautzky-Willer A, Harreiter J, Pacini G. Sex and gender differences in risk, pathophysiology and complications of type 2 diabetes mellitus. Endocr Rev 2016; 37(3): 278-316. https://doi.org/10.1210/er.2015-1137
2. Shubrook JH, Chen W, Lim A. Evidence for the prevention of type 2 diabetes mellitus. J Am Osteopath Assoc 2018; 118(11): 730-737. https://doi.org/10.7556/jaoa.2018.158
3. Padhi S, Nayak AK, Behera A. Type II diabetes mellitus: a review on recent drug-based therapeutics. Biomed Pharmacother 2020; 131: 110708. https://doi.org/10.1016/j.biopha.2020.110708
4. Maruthur NM, Tseng E, Hutfless S, et al. Diabetes medications as monotherapy or Metformin-based combination therapy for type 2 diabetes: a systematic review and meta-analysis. Ann Intern Med 2016; 164(11): 740-751. https://doi.org/10.7326/M15-2650
5. Melzer Cohen C, Davis C, Shalev V, Chodick G. Effectiveness of vildagliptin as add-on to Metformin monotherapy among uncontrolled type 2 diabetes mellitus patients in a real-world setting. J Diabetes 2018; 10(1): 68-72. https://doi.org/10.1111/1753-0407.12560
6. Wang Z, Sun J, Han R, et al. Efficacy and safety of sodium-glucose cotransporter-2 inhibitors versus dipeptidyl peptidase-4 inhibitors as monotherapy or add-on to Metformin in patients with type 2 diabetes mellitus: a systematic review and meta-analysis. Diabetes Obes Metab 2018; 20(1): 113-120. https://doi.org/10.1111/dom.13047
7. Zhou Y, Geng Z, Wang X, Huang Y, Shen L, Wang Y. Meta-analysis on the efficacy and safety of SGLT2 inhibitors and incretin based agents combination therapy vs. SGLT2i alone or add-on to Metformin in type 2 diabetes. Diabetes Metab Res Rev 2020; 36(2): e3223. https://doi.org/10.1002/dmrr.3223
8. Singh AK, Singh R, Khunti K. Comment on Gan et al. Efficacy of modern diabetes treatments DPP-4i, SGLT-2i, and GLP-1RA in white and Asian patients with diabetes: a systematic review and meta-analysis of randomized controlled trials. Diabetes Care 2020; 43(12): e200-e201. https://doi.org/10.2337/dc20-1950
9. Hagi K, Kochi K, Watada H, Kaku K, Ueki K. Effect of patient characteristics on the efficacy and safety of imeglimin monotherapy in Japanese patients with type 2 diabetes mellitus: A post-hoc analysis of two randomized, placebo-controlled trials. J Diabetes Investig 2023; 14(9): 1101-1109. https://doi.org/10.1111/jdi.14035.
10. Rohm TV, Meier DT, Olefsky JM, Donath MY. Inflammation in obesity, diabetes, and related disorders. Immunity 2022; 55(1): 31-55. https://doi.org/10.1016/j.immuni.2021.12.013
11. Dutta D, Jaisani R, Khandelwal D, Ghosh S, Malhotra R, Kalra S. Role of Metformin, sodium-glucose cotransporter-2 (SGLT2) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, and orlistat based multidrug therapy in glycemic control, weight loss, and euglycemia in diabesity: a real-world experience. Indian J Endocrinol Metab 2019; 23(4): 460-467. https://doi.org/10.4103/ijem.IJEM_185_19
12. Gilbert MP, Pratley RE. GLP-1 analogs and DPP-4 inhibitors in type 2 diabetes therapy: review of head-to-head clinical trials. Front Endocrinol 2020; 11: 178. https://doi.org/10.3389/fendo.2020.00178
13. Shaheer A, Kumar A, Menon P, Jallo M, Basha S. Effect of add-on therapy of sodium-glucose cotransporter 2 inhibitors and dipeptidyl peptidase 4 inhibitors on adipokines in type 2 diabetes mellitus. J Clin Med Res 2021; 13(6): 355-362. https://doi.org/10.14740/jocmr4510
14. Min SH, Yoon JH, Moon SJ, Hahn S, Cho YM. Combination of sodium-glucose cotransporter 2 inhibitor and dipeptidyl peptidase-4 inhibitor in type 2 diabetes: a systematic review with meta-analysis. Sci Rep 2018; 8(1): 4466. https://doi.org/10.1038/s41598-018-22658-2
15. Bashier A, Khalifa AA, Rashid F, et al. Efficacy and safety of SGLT2 inhibitors in reducing glycated hemoglobin and weight in Emirati patients with type 2 diabetes. J Clin Med Res 2017; 9(6): 499-507. https://doi.org/10.14740/jocmr2976w
16. Hsia DS, Grove O, Cefalu WT. An update on sodium-glucose co-transporter-2 inhibitors for the treatment of diabetes mellitus. Curr Opin Endocrinol Diabetes Obes 2017; 24(1): 73-79. https://doi.org/10.1097/MED.0000000000000311
17. Xu B, Li S, Kang B, Zhou J. The current role of sodium-glucose cotransporter 2 inhibitors in type 2 diabetes mellitus management. Cardiovasc Diabetol 2022; 21(1): 83. https://doi.org/10.1186/s12933-022-01512-w

18. Bailey CJ, Day C, Bellary S. Renal protection with SGLT2 inhibitors: effects in acute and chronic kidney disease. Curr Diab Rep 2022; 22(1): 39-52. https://doi.org/10.1007/s11892-021-01442-z
19. Lin SH, Cheng PC, Tu ST, Hsu SR, Cheng YC, Liu YH. Effect of Metformin monotherapy on serum lipid profile in statin-naïve individuals with newly diagnosed type 2 diabetes mellitus: a cohort study. PeerJ 2018; 6: e4578. https://doi.org/10.7717/peerj.4578
20. Rameshrad M, Razavi BM, Ferns GAA, Hosseinzadeh H. Pharmacology of dipeptidyl peptidase-4 inhibitors and its use in the management of metabolic syndrome: a comprehensive review on drug repositioning. Daru 2019; 27(1): 341-360. https://doi.org/10.1007/s40199-019-00238-7
21. Szekeres Z, Toth K, Szabados E. The effects of SGLT2 inhibitors on lipid metabolism. Metabolites 2021; 11(2): 87. https://doi.org/10.3390/metabo11020087