Asian Journal of Pharmaceutical and Health Sciences
www.ajphs.com

A Prospective Observational Study of Comparison, Safety, and Efficacy of Dipeptidyl Peptidase-4 Inhibitors for the Treatment of Type 2 Diabetes Mellitus in A Tertiary Care Hospital

Aneesa. N[1], Dilip Chandrasekhar[1]*, Jafer Chalil Parambil[2], Shamna.P.M[1], Fathima Thahseen[1]

1 Department of Pharmacy Practice, Alshifa College of Pharmacy, Perinthalmanna, Kerala, India.
2 Department of General Medicine, KIMS Al Shifa Hospital, Perinthalmanna, Kerala, India.

ARTICLE HISTORY

Received: 13.10.2022

Accepted: 07.11.2022

Available online: 31.12.2022

DOI:

10.5530/ajphs.2022.12.25

Keywords:

Type 2 Diabetes Mellitus, Dipeptidyl peptidase-4 inhibitors, Teneligliptin.

***Corresponding author:**

Email : dilipc@alshifacollegeofpharmacy.ac.in
Phone : +91 -

ABSTRACT

The purpose of the study was to determine the safety and efficacy of Dipeptidyl Peptidase 4-Inhibitor as mono-therapy and in combination therapy. The impact of age, disease duration and gender on the efficacy of DPP-4 inhibitors were also studied.

A prospective observational study was conducted among patients with type 2 diabetes mellitus. The study consisted of 6 groups: Metformin + Glimepiride, Metformin + Teneligliptin, Glimepiride + Teneligliptin, Metformin only, Teneligliptin only and Glimepiride only. Fasting and Post Prandial Blood Sugar and HbA1c were monitored before and after 6 months of therapy.

In combination therapy, the adverse effects were higher in Glimepiride and Teneligliptin group followed by Metformin and Glimepiride and Metformin and Teneligliptin. The mean FBS reduction was 21.57 mg/dl, 28.32 mg/dl, and 20.08mg/dl in Metformin + Glimepiride, Metformin + Teneligliptin and Glimepiride + Teneligliptin, respectively. The mean Post-Prandial Blood Sugar reduction was 27.63mg/dl, 42.78mg/dl, 34.13mg/dl in Metformin + Glimepiride, Metformin + Teneligliptin and Glimepiride + Teneligliptin, respectively. The mean HbA1c reduction was 1.30%, 1.41%, and 0.80% in Metformin + Glimepiride, Metformin + Teneligliptin and Glimepiride + Teneligliptin, respectively.

Metformin and Teneligliptin combination therapy and Teneligliptin monotherapy were safe and efficacious compared to all other oral hypoglycemic drugs under study. There was no significant impact of gender, BMI class and disease duration on the drug's efficacy.

INTRODUCTION

Diabetes Mellitus (DM) is a group of metabolic disorders characterized by hyperglycemia and abnormalities in carbohydrate, fat, and protein metabolism.[1] The most common endocrine disorder, characterized by hyperglycemia, is featured by impaired insulin secretion with or without insulin resistance.[2] According to International Diabetes Federation (IDF), 425 million people in the world have diabetes. A recent report stated that 72,946,400 cases in India (adult diabetes prevalence, 8.8%) and still growing. Kerala, the diabetes capital, is far ahead in the prevalence (20%) of the country. There are several studies from different parts of Kerala depicting an upward slope. A study from the central part of Kerala reported an 11% prevalence of pre-diabetes.[3]

Type 2 diabetes (T2DM) is more compared to type 1 diabetes (T1DM).[4] Diagnosed T2DM increases with age and decreased with educational advancement. Drastic augmentation of mortality has demanded appropriate diabetic treatment at an affordable cost. Many drugs are utilized and even newer agents are launched. In order to bring out optimal management, mutual comparison of anti-diabetic drugs is essential. Di- Peptidyl Peptidase-4 (DPP-4) Inhibitors are newer agents that work by inactivating the incretin hormones, Glucagon-like Peptide- 1 (GLP-1) and Glucose Inhibitory Peptide (GIP) action and are

involved in insulin secretion cascade initiation following a meal. The enzyme is a serine protease that reduces GLP-1, resulting in a small half-life of the hormones. Thus, inhibition of DPP-4 increases incretin hormones' half-life and eventually elevates insulin secretion.

DPP-4 inhibitors partially reduce the inappropriately elevated glucagon postprandial and stimulate glucose-dependent insulin secretion. Since Teneligliptin is a newer drug, more studies are needed to determine its safety and efficacy. A longer half-life, dual mode of elimination, and cost-effectiveness compared to other Gliptins, resulted in their profound prescription pattern now days.[5] Hence, we can compare the agent with Metformin and Glimepiride, another most utilized drugs.[6]

The use of DPP-4 inhibitors was suggested on the background of the extreme DPP-4 mediated GLP-1 degradation in diabetic patients. It was possible to completely preserve exogenous and endogenous GLP-1 and thereby enhancing its insulinotropic activity. This study aimed to determine the safety and efficacy of Teneligliptin in T2DM and assess the impact of age, disease duration and gender on the efficacy of DPP-4 inhibitors.

MATERIALS AND METHODS

A prospective observational study was conducted from October 2018 to August 2019 to assess the safety and efficacy of DPP-4 inhibitors (Teneligliptin) in T2DM. In-patients and out-patients were recruited from General Medicine Department based on the selection criteria. This study was approved by the hospital's ethical committee as per letter no: KAS/ EC/2018-36, and official consent was also obtained for carrying out the research. The purpose and nature of the study were explained to each participant through face-to-face interviews and telephonic calls which provided enough time for clarifications. Written informed consent was obtained after understanding their willingness. Data were collected using a well-structured data collection form structurally designed to collect, record and measure details such as patient demographics, education status, lifestyle and diet, information on exercise and habits, disease and medication history, co-morbidities, adverse effects, and laboratory investigations. Moreover, medical records, researcher's observations, clinical rounds with the physician, and patient counselling served to impart more information.

The study was carried out in three phases. In the first phase, based on the therapeutic guidelines received from the general medicine physician, a therapeutic matrix was first identified in alignment with the aim and objectives of the study. Three combinations of three individual drugs were identified and were as follows: -

Group 1: patients receiving Metformin (1000-2000mg/day) and Glimepiride (1-3mg/day)

Group 2: patients receiving Metformin (1000-2000mg/day) and Teneligliptin (20-40mg/day)

Group 3: patients receiving Glimepiride (1-3mg/day) and Teneligliptin (20-40mg/day)

Group 4: patients receiving Metformin (1000-2000mg/day) only

Fig. 1 : Allocation of samples into 6 groups and the conduct of the study.

Group 5: patients receiving Teneligliptin (20-40 mg/day) only

Group 6: patients receiving Glimepiride (1-3mg/day) only

In the second phase, a criterion for including and excluding patients from the proposed study was formulated. Those of either gender, who were at least on one of the oral hypoglycemic agents (OHA) under investigation and those with good treatment compliance, were considered for the study. However, diabetic patients with psychiatric illnesses, drug abusers, alcoholics, and smokers were excluded.

Accordingly, the sample size was calculated by the equation: -

$$N = \frac{Z^2_{\alpha/2} \times P \times (1-P) \times D}{E^2}$$

Where Z α/2 = Normal deviate for two-tailed hypothesis, D=precision, P= anticipated proportion, E = Margin of error

We obtained a total of 231 patients on compliance with the selection criteria and were enrolled in the study. The description of the disease, type of diabetes, causes, signs and symptoms, risk factors, early identification, treatment, medication adherence, precautions to be taken, diet control, and exercises, concerning each participant were documented. The adverse drug reactions (ADR) encountered during the study were scored using Naranjo adverse drug reaction probability scale and documented. A leaflet was prepared and distributed to patients and each of our participants was counselled on the disease, drugs, and required lifestyle changes.

The study population's fasting blood sugar (FBS), post-prandial blood sugar (PPBS) and glycosylated haemoglobin (HbA1c) were repeatedly measured before and after 6 months of initiating the oral hypoglycemic agents under investigation. Before starting the anti-diabetic drugs, the patient's sugar level (FBS, PPBS, HbA1c) gave the pre-OHA treatment value and the post-OHA treatment after 6 months of treatment. The difference between pre-OHA treatment and post-OHA treatment represents the change in glycemic level or the effectiveness of OHA, the primary study outcome (Figure 1).

Finally, in the third phase, values confined to socio-demographic and disease factors and glycemic levels were entered into Microsoft Excel. The frequency and percentage of each variable were documented, and the mean (standard deviation) was calculated from the patient's FBS, PPBS and HbA1c. These were then exported to SPSS version 26, and likelihood ratio and Chi-square test were employed to associate different variables (p-value <0.05). T-test and one-way ANOVA were quantified to find the difference between the samples in the groups.

RESULTS

A total of 231 patients were enrolled upon grant of informed consent and those met the inclusion and exclusion criteria. Based on the treatment regimen, patients were categorized into 6 groups. Group 1 (Metformin + Glimepiride), Group 2 (Metformin + Teneligliptin), Group 3(Glimepiride + Teneligliptin), Group 4 (Metformin), Group 5 (Teneligliptin), and Group 6 (Glimepiride)

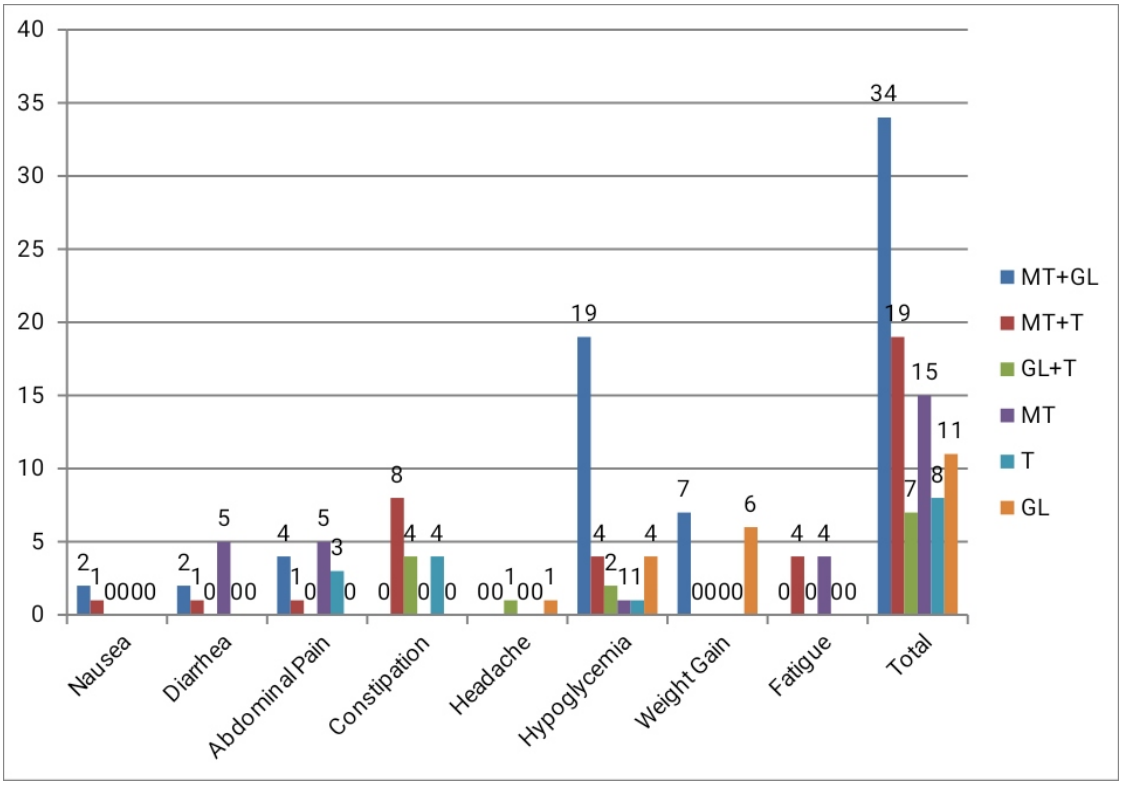

Fig. 2 : UAdverse drug reactions reported with different anti-diabetic drug regimens.

MT+GL, Metformin+Glimepiride; MT+T, Metformin+Teneligliptin; GL+T, Glimepiride+Teneligliptin; MT, Metformin; T, Teneligliptin; GL, Glimepiride.

constituted 66, 64, 9, 51, 23, and 18 patients, respectively.The patient's sociodemographic and disease-related factors are represented in Table 1. We observed more patient with age less than 60 years, were provided with Metformin and Glimepiride (group 1, n=30, 45.5%), Metformin and Teneligliptin (group 2, n=37, 57.8%) and Metformin only (group 4, n=22, 43%). However, patients on Glimepiride and Teneligliptin (group 3, n=5, 55.6%) and Glimepiride only (group 6, n=10, 55.6%) were predominant in the age group between 70 to 60 years. The likelihood ratio was employed to associate the patient's age with different treatment groups and it was found to be statistically significant (p-value <0.01). Hence, all the samples in the group are not the same.

Female populations were abundant in Metformin and Glimepiride (group 1, n=44, 66.7%), Glimepiride and Teneligliptin (group 3, n=6, 66.7%), Metformin only (group 4, n=28, 54.9%), Teneligliptin only (group 5, n=18, 78.3%) and Glimepiride only subsets (group 6, n=12, 66.7%). Most of our patients were non-vegetarian and observed to have overweight. When we analyzed their life status, very few active patients pooled in Metformin and Glimepiride (group 1, n=6) and Metformin and Teneligliptin population (group 2, n=5), but the majority were lesser active. Profound patients in all the treatment groups had restricted themselves from sweet food. We noticed a high level of familial history, greater aggregate in patients on Metformin and Glimepiride (group 1, n=45, 68%) and least in Metformin only (group 4, n=23, 45%).

Most patients on Metformin and Glimepiride (n=23), Glimepiride and Teneligliptin (n=4), Teneligliptin only (n=11) and Glimepiride only (n=8), and Metformin and Teneligliptin (n=37), Metformin only (n=22) were bearing diabetes for 5 to 10 years and less than 5 years, respectively. The retrieved data

Table 1 : Sociodemographic and disease related factors of patients treated with different anti-diabetic drug regimens.

Socio demographic factors		Frequency (%)											
		Group1		Group 2		Group 3		Group 4		Group 5		Group 6	
		MT+GL		MT+T		GL+T		MT		T		GL	
		n	%	n	%	n	%	n	%	n	%	n	%
Age(years)	> 70	16	24.24	9	14.06	2	22.22	12	23.53	10	43.48	6	33.33
	70-60	20	30.30	18	28.13	5	55.56	17	33.33	8	34.78	10	55.56
	<60	30	45.45	37	57.81	2	22.22	22	43.14	5	21.74	2	11.11
Gender	Male	22	33.33	33	51.56	3	33.33	23	45.10	5	21.74	6	33.33
	Female	44	66.67	31	48.44	6	66.67	28	54.90	18	78.26	12	66.67
BMI (Kg/m^2) *	Obese	8	12.12	6	9.38	1	11.11	3	5.88	3	13.04	4	22.22
	Overweight	30	45.45	31	48.44	4	44.44	27	52.94	13	56.52	7	38.89
	Under weightor normal	28	42.42	27	42.19	4	44.44	21	41.18	7	30.43	7	38.89
Educational Qualification	Graduate	10	15.15	3	4.69	0	0.00	6	11.76	1	4.35	2	11.11
	2° Education	11	16.67	9	14.06	3	33.33	11	21.57	2	8.70	4	22.22
	1° Education	22	33.33	21	32.81	4	44.44	22	43.14	15	65.22	9	50.00
	No	23	34.85	31	48.44	2	22.22	12	23.53	5	21.74	3	16.67
Dietary intake	Vegetarian	17	25.76	21	32.81	3	33.33	16	31.37	7	30.43	8	44.44
	Non-Vegetarian	49	74.24	43	67.19	6	66.67	35	68.63	16	69.57	10	55.56
Diet Control	Full-fledged	21	31.82	28	43.75	4	44.44	14	27.45	9	39.13	4	22.22
	No	45	68.18	36	56.25	5	55.56	37	72.55	14	60.87	14	77.78
Life style	Highly Active	6	9.09	5	7.81	0	0.00	0	0.00	0	0.00	0	0.00
	Active	17	25.76	13	20.31	2	22.22	12	23.53	5	21.74	3	16.67
	Less Active	30	45.45	25	39.06	5	55.56	29	56.86	12	52.17	11	61.11
	Sedentary	13	19.70	21	32.81	2	22.22	10	19.61	6	26.09	4	22.22
Exercise	Yes	27	40.91	18	28.13	2	22.22	12	23.53	6	26.09	5	27.78
	No	39	59.09	46	71.88	7	77.78	39	76.47	17	73.91	13	72.22

Sweet Food Consumption	Yes	18	27.27	27	42.19	3	33.33	21	41.18	8	34.78	5	27.78
	No	48	72.73	37	57.81	6	66.67	30	58.82	15	65.22	13	72.22
Family History	Yes	45	68.18	44	68.75	5	55.56	23	45.10	14	60.87	12	66.67
	No	21	31.82	20	31.25	4	44.44	28	54.90	9	39.13	6	33.33
Genetic Predisposition to DM	Father	12	18.18	11	17.19	2	22.22	10	19.61	6	26.09	4	22.22
	Mother	30	45.45	24	37.50	2	22.22	9	17.65	5	21.74	5	27.78
	Both	4	6.06	9	14.06	1	11.11	4	7.84	3	13.04	3	16.67
	No	20	30.30	20	31.25	4	44.44	28	54.90	9	39.13	6	33.33
Duration of DM (years)	<5	21	31.82	37	57.81	2	22.22	22	43.14	6	26.09	6	33.33
	5-10	23	34.85	20	31.25	4	44.44	16	31.37	11	47.83	8	44.44
	11-15	12	18.18	4	6.25	2	22.22	8	15.69	3	13.04	2	11.11
	>15	10	15.15	3	4.69	1	11.11	5	9.80	3	13.04	2	11.11
Incidence of Co-morbidities	Yes	39	59.09	46	71.88	6	66.67	28	54.90	14	60.87	11	61.11
	No	27	40.91	18	28.13	3	33.33	23	45.10	9	39.13	7	38.89
Micro vascular complications	Cardiovascular disease	4	36.36	5	41.67	1	100	2	66.67	3	75.00	2	66.67
	Hypertension	4	36.36	5	41.67	0	0	1	33.33	1	25.00	1	33.33
	Peripheral vascular disease	3	27.27	2	16.67	0	0	0	0.00	0	0.00	0	0.00
Macro vascular complications	Retinopathy	22	68.75	18	50.00	2	40.00	19	76.00	5	45.45	6	75.00
	Nephropathy	10	31.25	12	33.33	3	60.00	6	24.00	6	54.55	2	25.00
	Neuropathy	0	0.00	6	16.67	0	0.00	0	0.00	0	0.00	0	0.00
DM and Co-morbidities	Before DM	11	28.21	22	47.83	0	0.00	5	17.86	2	14.29	0	0.00
	After DM	20	51.28	17	36.96	3	50.00	12	42.86	8	57.14	4	36.36
	Same time	6	15.38	3	6.52	2	33.33	5	17.86	2	14.29	4	36.36
	Unknown	2	5.13	4	8.70	1	16.67	6	21.43	2	14.29	3	27.27

MT+GL, Metformin+Glimepiride; MT+T, Metformin+Teneligliptin; GL+T, Glimepiride+Teneligliptin; MT, Metformin; T, Teneligliptin; GL, Glimepiride.

showed that most patients on Metformin and Glimepiride (group1, n=20, 51.3%), Glimepiride and Teneligliptin (group 3, n=3, 50%), Metformin only (group 4, n=12, 43.9%), Teneligliptin only (group 5, n=8, 57.1%) and Glimepiride only (group 6, n=4, 36.7%) had symptoms of other disease conditions after the diabetes incidence. Only in Metformin and Teneligliptin treatment population (group 2, n=22, 47.8%), there were more patients with co-morbidities before diabetes. The likelihood ratio was utilized to find the association between the variation of incidence among diabetes and co-morbidities with different treatment groups. There was statistical significance between the two variables, and the samples are said to be different (p-value <0.01).Both the diabetic micro-vascular and macro-vascular complications were taken into consideration. It was identified that a few patients across the treatment groups had cardiovascular diseases, hypertension, and peripheral vascular diseases. However, retinopathy was prominent in Metformin and Glimepiride (group 1, n=22, 68.8%), Metformin and Teneligliptin (group 2, n=18, 50%), Metformin only (group 4, n=19, 76%) and Glimepiride only (group 6, n=6, 75%) treated patients. Nephropathy and neuropathy were profound among those on Teneligliptin only (group 5, n=6, 54.6%) and Metformin and Teneligliptin (group 2, n=12, 33.3%), respectively. The likelihood ratio was calculated for macrovascular complications with different treatment groups and was statistically significant (p-value <0.05).

We reported 94 probable adverse drug reactions; nausea, diarrhoea and abdominal pain, constipation, headache, hypoglycemia, weight gain, and fatigue was identified and are presented in Figure 2. The patient's group on Metformin and Glimepiride reported more ADR (n=34, 36.2%) compared to other groups (group2, n=19, 20.2%; group 3, n=7, 7.4%; group 4, n=15, 14.9%; group 5, n=8, 8.5% and group 6, n=11, 11.7%).

Metformin and Teneligliptin (28.33±4.88) had the highest mean FBS reduction ability followed by Metformin and Glimepiride (21.57±9.59) and Glimepiride and Teneligliptin (20.9±0.85), in our population. Despite the better efficacy of combination agents, individual drugs also had an appreciable impact on the patient's outcome. Teneligliptin alone (mean [SD]= 18.54[1.01]) had depicted significant FBS lowering property than individual OHAs such as Metformin (mean [SD]= 16.10[0.54]) and Glimepiride (mean [SD]= 15.19[0.8]). The mean PPBS reduction was better portrayed by Metformin and Teneligliptin (42.77±2.6) followed by Glimepiride and Teneligliptin (34.13±0.66) and Teneligliptin alone (32.10±1.12). A similar pattern was identified concerning the reduction in mean HbA1c; Metformin and Teneligliptin (1.41±0.69) had lowered HbA1c better than other groups. However, Metformin and Glimepiride (1.30±0.54) administered patients reduced the glycosylated

Table 2 : Mean and standard deviation of Pre- and Post- glycemic level and effectiveness of different oral hypoglycemic agent's.

Parameters	Groups	Pre- OHA treatment		Post- OHA treatment		Change		"t"	p value
		Mean	S.D.	Mean	S.D.	Mean	S.D.		
FBS	MT+GL	184.55	35.03	162.98	33.85	21.57	9.59	18.28	< 0.001*
	MT+T	183.34	26.66	155.02	25.95	28.33	4.88	46.39	< 0.001*
	GL+T	177.24	10.19	157.16	10.33	20.09	0.85	70.60	< 0.001*
	MT	177.04	12.22	160.94	12.18	16.10	0.54	214.5	< 0.001*
	T	181.00	13.77	162.46	14.15	18.54	1.01	87.83	< 0.001*
	GL	178.49	13.07	163.29	13.15	15.19	0.80	80.25	< 0.001*
PPBS	MT+GL	200.84	32.37	173.22	29.80	27.62	9.41	23.83	< 0.001*
	MT+T	193.56	23.27	150.78	23.52	42.77	2.60	131.5	< 0.001*
	GL+T	184.14	9.87	150.01	10.19	34.13	0.66	154.4	< 0.001*
	MT	182.57	11.25	156.80	11.27	25.77	0.77	240.1	< 0.001*
	T	186.02	10.56	153.93	10.72	32.10	1.12	137.5	< 0.001*
	GL	185.72	8.57	162.49	8.95	23.22	1.00	98.78	< 0.001*
HbA1c	MT+GL	9.00	1.44	7.70	1.34	1.30	0.54	19.48	< 0.001*
	MT+T	8.54	1.45	7.12	1.54	1.41	0.69	16.43	< 0.001*
	GL+T	8.16	1.18	7.36	1.16	0.80	0.09	27.71	< 0.001*
	MT	8.23	1.00	7.09	0.96	1.13	0.22	37.47	< 0.001*
	T	8.32	1.21	7.58	1.25	0.74	0.18	20.33	< 0.001*
	GL	8.60	1.10	7.97	1.13	0.63	0.08	32.23	< 0.001*

*p<0.01

MT+GL, Metformin+Glimepiride; MT+T, Metformin+Teneligliptin; GL+T, Glimepiride+Teneligliptin; MT, Metformin; T, Teneligliptin; GL, Glimepiride.

Table 3 : Mean reduction in FBS, PPBS, HbA1c of patient's distributed based on age and duration of diabetes concerning each anti-diabetic therapies

Parameter, reduction in FBS, reduction in PPBS, reduction in HbA1C	Groups	Age			Duration of disease (Years)			
		> 70	60-70	< 60	<5	5-10	11-15	>15
		Mean±SD						
Reductionin FBS	MT+GL	18.66±7.84	21.32±9.61	23.33=10.27	20.73±11.5	21.37±8.1	24.04±8.6	20.80±10.4
	MT+T	28.06±4.10	27.87±5.53	28.61±4.83	27.79±4.1	29.54±6.4	27.52±4.7	27.83±0.7
	GL+T	20.10±0.14	19.76±0.99	20.90±0.14	20.90±0.1	19.60±1.1	20.20±0.3	20.20±0
	MT	16.11±0.13	16.05±0.77	16.14±0.47	16.13±0.5	16.11±0.7	16.01±0.4	16.10±0.2
	T	17.98±0.47*	18.71±0.63*	19.40=1.64*	19.17±1.6	18.48±0.7	18.30±0.4	17.77±0.7
	GL	15.87±0.94*	14.94±0.41*	14.45=0.78*	14.60±0.5*	15.21±0.4*	16.05±1.5*	16.05±1.1*
Reductionin PPBS	MT+GL	25.68±8.13	28.60±8.08	28.01=10.90	24.26±9.7	31.21±9.9	25.27±6.2	29.25±8.6
	MT+T	41.82±3.33	43.00±2.31	42.89±2.57	42.91±2.8	42.67±2.6	42.63±2.3	41.93±0.1
	GL+T	34.10±0	34.02±0.84	34.45±0.64	34.45±0.6	34.03±1	34.05±0.1	34.10±0
	MT	25.75±1.16	25.74±0.22	25.81±0.81	25.80±0.8	25.64±0.5	26.09±1.2	25.56±0.3
	T	32.80±1.02*	31.70±0.52*	31.32=1.32*	31.57±1.3	32.03±0.8	32.10±0.4	33.40±1.6
	GL	22.65±1.01	23.58±0.97	23.15±0.21	23.18±0.4	23.48±1.1	23.65±0.2	21.90±0.6
Reductionin HbA1c	MT+GL	1.42±0.63	1.27±0.43	1.27=0.57	1.18±0.5	1.43±0.6	1.23±0.3	1.36±0.7
	MT+T	1.80±1.63	1.20±0.30	1.42=0.34	1.39=0.4[¶]	1.22±0.3[¶]	1.40±0.2[¶]	3.00±2.7[¶]
	GL+T	0.70±0.14	0.84±0.05	0.80±0	0.80=0	0.85±0.1	0.70±0.1	0.80±0
	MT	1.13±0.19	1.12±0.23	1.15±0.23	1.13±0.2	1.15±0.3	1.15±0.2	1.08±0.2
	T	0.69±0.09	0.85±0.21	0.68±0.19	0.67±0.2	0.80±0.2	0.70±0.1	0.73±0.1
	GL	0.57±0.08*	0.67±0.07*	0.60±0*	0.67±0.1	0.64±0.1	0.55±0.1	0.55±0.1

*p<0.05;

¶p<0.01;

MT+GL, Metformin+Glimepiride; MT+T, Metformin+Teneligliptin; GL+T, Glimepiride+Teneligliptin; MT, Metformin; T, Teneligliptin; GL, Glimepiride.

haemoglobin than Glimepiride and Teneligliptin treated group (0.80±0.09). Metformin alone (1.13±0.22) showed an excellent favorable response concerning HbA1c compared to the Teneligliptin alone (0.74±0.18) and Glimepiride alone (0.63±0.08). The paired "t" test was used to compare each group's pre and post-measurements of FBS, PPBS, and HbA1c. There was a difference ($p < 0.05$) in FBS, PPBS, and HbA1c for all the groups (Table 2).

The one-way ANOVA test was used to compare the reduction in FBS, PPBS, and HbA1c according to age (Years) for each group. There was a difference in the reduction of FBS for Teneligliptin group ($p = 0.023$) and Glimepiride group ($p = 0.02$). In the Teneligliptin group, the mean FBS was prominently lowered in patients younger than 60 years (17.95±0.47). However, Glimepiride had a high impact on patients with an age greater than 70 years (15.87±0.97), considering the FBS. The reduction in PPBS differed in Teneligliptin group ($p = 0.017$) and the HbA1c differed in Glimepiride ($p = 0.035$) group according to age (Table 3). Accordingly, there was a better lowering of PPBS in patients with age greater than 70 years (32.80±1.02), treated with Teneligliptin. Those managed with Metformin only had a significant impact on patients with ages between 60 to 70 (0.67±0.07).Similarly, one-way ANOVA was computed to analyze the reduction in FBS, PPBS, and HbA1c according to the duration of the disease (Years). There was a difference in reduction in FBS for the Glimepiride group ($p = 0.03$), and HbA1c for the Metformin and Teneligliptin group ($p < 0.001$) according to the duration of disease. It was noticed that when the duration of diabetes increased, there was an increase in the reduction of patients' FBS in the Glimepiride group. A similar pattern was noticed in Metformin and Teneligliptin-treated patients. The Independent sample "t" test was used to compare changes in FBS, PPBS, and HbA1c according to gender. There was no difference ($p > 0.05$) in the changes according to gender for each group.

DISCUSSION

American Diabetes Association guidelines recommend Metformin to be the first-line choice for T2DM. If glycemic control is not achieved, add-on agents such as Sulfonylurea, DPP-4 inhibitor or other OHAs or Insulin need to be considered. Despite the effectiveness of Metformin, the emergence of newer anti-diabetic drugs necessitates the comparison with their benefits. India is a developing country, and efficacious, safe and cost-effective OHA like Glimepiride is apt to be the first add-on therapy to Metformin.[7] Thus, we included Metformin and Glimepiride as a comparison group in the study. DPP-4 inhibitors are a well-established OHA class that was limited because of their high cost. However, Teneligliptin was found to be cost-effective.[8] Continuous research would strengthen the evidence to utilize the drug effectively.[9]

Metformin alone or combined with Glimepiride or Teneligliptin were prescribed for younger patients, evidencing the use of these drugs in early treatment. However, preference for Glimepiride and Teneligliptin went to those between 60 to70 age groups, indicating the combination to be used when other OHAs failed or not responding. Whereas, Teneligliptin were of choice to older patients. Patient gender-wise distribution revealed a greater pooling of the female population in the region.In the current study, among the combination therapy, the incidence of adverse effects was higher in Glimepiride and Teneligliptin group (77%) followed by Metformin and Glimepiride (51%) and least in Glimepiride and Teneligliptin (29%). Hypoglycemia (19 patients) and weight gain (7 patients) were major ADRs in Metformin and Glimepiride group, and identical findings were observed by Hye Soon Kim *et al*.[10] In Metformin and Teneligliptin group, the main ADRs were constipation (8 patients) and hypoglycemia (4 patients) and resembled the report developed by Kadowak T and kondo K and also in a drug update by Kharkar S.[11,12] Similarly, Glimepiride and Teneligliptin group also showed constipation (4 patients) and hypoglycemia (2 patients), as major ADRs.[13] While considering mono-therapy, the rate of incidence of adverse effects was higher with Glimepiride (61.1%) followed by Teneligliptin (34.8%) and Metformin (29.4%). The main adverse events showed by Metformin were diarrhoea (5 patients), stomach upset (5 patients) and weakness (4 patients) and this observation was supported by Hamid Nasri and Mahmud Rafieian Kopaei.[14] In the Teneligliptin group, significant events were constipation (4 patients), abdominal discomfort (3 patients) and hypoglycemia (1 patient). Predominant ADR noted on Glimepiride was weight gain (6 patients) and hypoglycemia (6 patients), and this was supported by research conducted by Abdul Basit *et al*.[15] All the adverse drug reactions were mild and did not warrant medication change or hospital admission.

Our study reported a significant decrease in mean FBS, mean PPBS and mean HbA1c in all patients either with monotherapy or combination therapy. After 6 months of dual therapy, mean FBS reduction ($p<0.001$) was 28.33 mg/dl, 21.57 mg/dl, and 20.09mg/dl in Metformin and Teneligliptin, Metformin and Glimepiride and Glimepiride and Teneligliptin groups, respectively. Indicating better treatment efficacy in terms of FBS among those treated with Metformin and Teneligliptin and similar inferences was coined by T.Nishanth *et al*.*[16]* The mean PPBS reduction after 6 months of therapy ($p<0.001$) was 42.77mg/dl, 34.13mg/dl and 27.62mg/dl in Metformin and Teneligliptin, Glimepiride and Teneligliptin and Metformin and Glimepiride group, respectively. This points out a more significant PPBS reduction in the two-combination therapy containing Teneligliptin, and evidence from M.K Kim *et al*. strengthens our findings.*[17,18]* After 6 months of treatment, the mean HbA1c reduction ($p<0.001$) was 1.41%, 1.30%, and 0.80% in Metformin and Teneligliptin, Metformin and Glimepiride and Glimepiride and Teneligliptin groups, respectively. Finally, when we combine the above results, the combination therapy with Metformin and Teneligliptin is projected to be most efficacious, followed by Metformin and Glimepiride, and Glimepiride and Teneligliptin.[19] Significant reduction in hyperglycemia was seen in these groups and the study results are similar to the conclusions depicted by Shashikala E *et al*.[20]

Mono-therapy with Teneligliptin appreciably decreased the FBS and PPBS much more than Metformin and Glimepiride. However, HbA1c reduction was dominant in the Metformin group. BMI did not influence our patient's PPBS, FBS and HbA1c (p- value>0.05). Even though T2DM and obesity are highly interred related from both pathophysiological and epidemiological standpoints, it should be noted. The difference between normal and obese from a diabetes treatment viewpoint can hardly be traced. This tends to a void in the perception of the efficacy of the OHA's among obese diabetics, and the observation was similar to a study conducted by Xiaoling Cai *et al*.[21] In the current study, the data obtained showed little to insignificant change in PPBS, FBS, and HbA1c among the diabetes duration subgroups. This skewness can be explained due to recollection

bias by the patient and lack of proper documents in order to validate information provided by the patient. The presence of a duly updated database significantly increases the scope to identify, analyze and carryout timely treatment intervention promptly. This result was contradictory to the study conducted by Yuji Tajiri *et al*.[22] The current study revealed changes in the reduction of PPBS, FBS and HbA1c among males and females in the different drug groups. There were variations across groups, hence it could not be determined. The results support the concept that was found earlier. Male diabetics had commendable glycemic control and were observed with lesser depression, anxiety, and enthusiasm. Previous studies revealed that the quality of glycemic control was worse in women than men of in all ages. Several studies showed poor glycemic control among women, attributed to the burden of carrying out daily household chores. This observation is contrary to the study conducted by Yuji Tajiri. Detailed studies are required to determine the exact influence of gender, BMI, and disease duration on drug efficacy.

Teneligliptin proved to be more effective than the commonly prescribed Glimepiride. Patients must have ready access to pharmaceutical care services like patient counseling, since diabetes is the most physically and behaviorally demanding chronic disorder. Patients should be informed appropriately that diabetes cannot be cured and can be controlled.[23] The current open observational study was carried out in a population sampled using the convenience method. Even in such a limited setting, the result found was significant, both statistically and in terms of treatment outcome. The shortcomings of the study design are evident. However, the result yielded was quite promising. A controlled study with larger samples will surely generate more noticeable results on Teneligliptin's efficacy. This suggests clinical pharmacists' importance in the new era. A pharmacist with updated knowledge and skill would be able to perform tasks that impart better patient care.

CONCLUSION

The results obtained from the study reveal that certain drugs and drug combinations work better than others. It was observed that Teneligliptin monotherapy works better than Glimepiride and Metformin+Teneligliptin combination showed better glycemic control than the other groups in the study. Metformin, an oral biguanide has been prescribed for diabetic treatment since 1957. Teneligliptin was recently introduced in the year 2012. From the present study, it is evident that these two diabetic medications introduced 55 years apart picturized more efficacy with combination therapies than monotherapy. It clarifies that improving treatment outcomes by carefully optimizing treatment regimens is equally or perhaps more important than introducing new medications or treatment methods. During the study, counseling was provided to all patients. The patients expressed positive feedback towards counseling indicating proper guidance from a clinical pharmacist is also required.

ACKNOWLEDGEMENT

This study was perfomed as part of the general medicine department under Dr.Jafer of KIMS Al-shifa hospital.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

ADR: Adverse Drug Reaction; BMI: Body Mass Index; DPP-4: Dipeptidyl Peptidase-4; FBS: Fasting Blood Sugar; GI: Gastro Intestine; GIP: Glucose-Dependent Insulinotropic Polypeptide; GLP-1: Glucagon-Like Peptide-1; HbA1c: Hemoglobin A1c; OHAD: Oral Hypoglycemic Agents; PPBS: Post Prandial Blood Sugar; SPSS: Statistical Package for Social Sciences; T1DM: Type 1 Diabetes Mellitus; T2DM: Type 2 Diabetes Mellitus.

REFERENCES

1. Wells BG, DiPiro JT, Schwinghammer TL, DiPiro CV. Pharmacotherapy handbook. 9th ed. Vol. 976; n.d.
2. Walker R, Whittlesea C, editors. Clinical pharmacy and therapeutics. 5th ed. Edinburgh: Churchill Livingstone/ Elsevier; 2012.
3. Diabetes in Kerala | Cadi n.d. [cited Aug 6, 2021] Available from: https://cadiresearch.org/topic/diabetes-indians/diabetes-keralal.
4. Bullard KM, Cowie CC, Lessem SE, Saydah SH, Menke A, Geiss LS, *et al*. Prevalence of diagnosed diabetes in adults by diabetes type - United States, 2016. MMWR Morb Mortal Wkly Rep. 2018;67(12):359-61. doi: 10.15585/mmwr.mm6712a2, PMID 29596402.
5. Ceriello A, De Nigris V, Iijima H, Matsui T, Gouda M. The unique pharmacological and pharmacokinetic profile of teneligliptin: implications for clinical practice. Drugs. 2019;79(7):733-50. doi: 10.1007/s40265-019-01086-0, PMID 30982160.
6. Sharma SK, Panneerselvam A, Singh KP, Parmar G, Gadge P, Swami OC. Teneligliptin in management of type 2 diabetes mellitus. Diabetes Metab Syndr Obes. 2016;9:251-60. doi: 10.2147/DMSO.S106133, PMID 27574456.
7. Kalra S, Aamir AH, Raza A, Das AK, Azad Khan AK, Shrestha D, *et al*. Place of sulfonylureas in the management of type 2 diabetes mellitus in South Asia: A consensus statement. Indian J Endocrinol Metab. 2015;19(5):577-96. doi: 10.4103/2230-8210.163171, PMID 26425465.
8. June_2020_issue.pdf n.d.
9. Garber AJ, Abrahamson MJ, Barzilay JI, Blonde L, Bloomgarden ZT, Bush MA, *et al*. Consensus statement by the American Association of Clinical Endocrinologists and American college of endocrinology on the comprehensive Type 2 diabetes management algorithm--2016 executive summary. Endocr Pract. 2016;22(1):84-113. doi: 10.4158/EP151126.CS, PMID 26731084.
10. Kim HS, Kim DM, Cha BS, Park TS, Kim KA, Kim DL, *et al*. Efficacy of glimepiride/metformin fixed-dose combination vs metformin uptitration in type 2 diabetic patients inadequately controlled on low-dose metformin monotherapy: A randomized, open label, parallel group, multicenter study in Korea. J Diabetes Investig. 2014;5(6):701-8. doi: 10.1111/jdi.12201, PMID 25422771.
11. A New DPP-4 inhibitor for Type 2 Diabetes. 2016;21:4.
12. Kadowaki T, Kondo K. Efficacy and safety of teneligliptin added to glimepiride in Japanese patients with type 2 diabetes mellitus: a randomized, double-blind, placebo-controlled study with an open-label, long-term extension. Diabetes Obes Metab. 2014;16(5):418-25. doi: 10.1111/dom. 12235, PMID 24205974.
13. Kadowaki T, Haneda M, Ito H, Ueno M, Matsukawa M,

Yamakura T, *et al*. Safety and efficacy of long-term treatment with teneligliptin: Interim analysis of a post-marketing surveillance of more than 10,000 Japanese patients with type 2 diabetes mellitus. Expert Opin Pharmacother. 2018;19(2):83-91. doi: 10.1080/ 14656566. 2017.1420165, PMID 29268035.

14. Nasri H, Rafieian-Kopaei M. Metformin: Current knowledge. J Res Med Sci. 2014;19(7):658-64. PMID 25364368.
15. Basit A, Riaz M, Fawwad A. Glimepiride: evidence-based facts, trends, and observations (GIFTS) Vasc Health Risk Manag. 2012;8:463-72. doi: 10.2147/HIV.S33194, PMID 23028231.
16. Nishanth T, Maheshwari CU, Lakshmi RS, Sri D, Goud P, Tabassum K, *et al*. A study to compare efficacy of metformin-glimepiride versus metformin-teneligliptin in type II diabetic patients. IJPSR n.d.; 9.
17. Kim MK, Rhee EJ, Han KA, Woo AC, Lee MK, Ku BJ, *et al*. Efficacy and safety of teneligliptin, a dipeptidyl peptidase-4 inhibitor, combined with metformin in Korean patients with type 2 diabetes mellitus: a 16-week, randomized, double-blind, placebo-controlled phase III trial. Diabetes Obes Metab. 2015;17(3):309-12. doi: 10.1111/dom.12424, PMID 25475929.
18. Gadge P, Gadge R, Paralkar N. Patients characteristics associated with better glycemic response to teneligliptin and metformin therapy in type 2 diabetes: a retrospective study. Int J Adv Med. 2018;5:424:ijam20181082. doi: 10.18203/2349- 3933.
19. Zhu H, Zhu S, Zhang X, Guo Y, Shi Y, Chen Z, *et al*. Comparative efficacy of glimepiride and metformin in monotherapy of type 2 diabetes mellitus: meta-analysis of randomized controlled trials. Diabetol Metab Syndr. 2013;5(1):70. doi: 10.1186/1758-5996-5-70, PMID 24228743.
20. E. S, B. N. V. RR. Study of glycemic response of oral anti-diabetic drugs in type 2 diabetic patients. Int J Res Med Sci. 2018;6(2):645. doi: 10.18203/2320-6012.ijrms20180314.
21. Cai X, Yang W, Gao X, Zhou L, Han X, Ji L. Baseline body mass index and the efficacy of hypoglycemic treatment in Type 2 diabetes: A meta-analysis. PLOS ONE. 2016;11 (12):e0166625. doi: 10.1371/journal.pone.0166625, PMID 27935975.
22. Tajiri Y, Tsuruta M, Ohki T, Kato T, Sasaki Y, Tanaka K, *et al*. Long-term efficacy of sitagliptin for the treatment of type 2 diabetic patients in Japan. Endocr J. 2012;59(3):197-204. doi: 10.1507/endocrj.ej11-0248, PMID 22156327.
23. Professional Practice Committee. Standards of medical care in diabetes2018. Dia Care. 2018;41(Suppl 1):S3-. doi: 10.2337/dc18-Sppc01, PMID 29222370.

Cite this article : Aneesa. N, Dilip Chandrasekhar, Jafer Chalil Parambil, Shamna, Riyaz, Fathimath Thasneem
A Prospective Observational Study of Comparison, Safety, and Efficacy of Dipeptidyl Peptidase-4 Inhibitors for the Treatment of Type 2 Diabetes Mellitus in A Tertiary Care Hospital
Asian J. Pharm. Hea. Sci.. 2022;12(1):2729-2738. DOI : 10.5530/ajphs.2022.12.25