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Comparison of Empagliflozin Versus Vildagliptin in Combination with Metformin in Individuals Diagnosed with Type II Diabetes Mellitus

Tayyaba Haroon[1], Maryam Jabeen[2], Romaiza Maqsood[3], Waqas Ahmed Baig[4], Zainab Shahab[1], Tahira Rafique[1]

[1]Abbas Institute of Medical Sciences, Muzaffarabad, AJK, Pakistan.
[2]Resident FCPS II Neurology, Federal Government Polyclinic Hospital, Islamabad, Pakistan.
[3]Allama Iqbal Teaching Memorial Hospital, Sialkot, Punjab, Pakistan.
[4]Cardiac Hospital, Muzaffarabad, AJK, Pakistan.

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Correspondence to: Tayyaba Haroon, Abbas Institute of Medical Sciences, Muzaffarabad, AJK, Pakistan.
Email: tayyabaharoon034@gmail.com

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ABSTRACT

Objective: To compare the outcome of combination of vildagliptin with metformin empagliflozin with metformin in individuals diagnosed with type II diabetes mellitus **Study design:** Randomized controlled trial. **Place and duration of study:** Department of Medicine, AIMS, Muzaffarabad, AJK from 21 January, 2025 to 15 June, 2025. **Methodology:** Three hundred and twenty individuals, fulfilled the selection criteria, were included. Then individuals were randomly allocated in 02 groups. In group-A, individuals were prescribed once daily oral empagliflozin plus metformin at the dose of 10/1000 mg. In group-B, individuals were prescribed once daily oral vildagliptin plus metformin at the dose of 50/1000 mg. At baseline and after 12 weeks of follow-up, HbA1c, fasting blood glucose level and lipid profile were assessed. Data was analyzed in SPSS v.25.0, with P–value ≤ 0.05 as significant. **Results:** In this trial, we enrolled total 320 individuals and randomized them in two equal group. The mean age of individuals enrolled in Group-A was 56.16 ± 9.57 years as well as in Group-B was 57.86 ± 9.33 years. In Group-A, there were 94 (58.8%) men and 66 (41.3%) women. In Group-B, there were 79 (49.4%) men and 81 (50.6%) women. The median change in HBA1c level in Group-A that was 0.80 (IQR: 0.78) % and in Group-B was 1.00 (IQR: 0.80) %. The median change in HBA1 was more achieve in Group-B, however the difference was insignificant (p>0.05). In Group-A, the median change in fasting blood glucose level of 20.00 (IQR: 37.50) vs. 25.00 (IQR: 46.75) mg/dl (p>0.05). The median change in total cholesterol level was 20.00 (IQR: 38.00) mg/dl vs. 28.00 (IQR: 31.00) mg/dl (p<0.05) and median change in triglycerides level was 28.00 (IQR: 40.00) vs. 29.00 (IQR: 79.00) mg/dl (p>0.05). **Conclusion:** The change in glycemic level and lipid profile of diabetic individuals is similar whether vildagliptin is given or empagliflozin is given in combination with metformin.

INTRODUCTION

Elevated hyperglycemia and the corresponding requirement to gradually increase medication in order to attain and maintain glycemic control are hallmarks of type 2 diabetes mellitus. It is suggested that hyperglycemia be treated with sequential therapy in order to provide a comprehensive evaluation of the effectiveness and risk-benefit ratio of each additional component.[1] The scientific justification for employing synergistic, contemporary pharmacological combination to accomplish glycemic objectives, postpone the degradation of glycemic control, and, consequently, perhaps maintain or slow down the deteriorating β-cell function, is, however, supported by a wealth of data.[2]

Endocrinologists commonly prescribe metformin to treat type II diabetes mellitus unless there is a contraindication. By blocking the liver's mitochondrial respiratory chain, it increases insulin sensitivity, activates AMP-activated protein kinase, and lowers cyclic adenosine monophosphate levels, which in turn lowers the production of gluconeogenic enzymes and keeps blood sugar levels in a euglycemic condition..[3, 4] The primary transport protein in renal proximal convoluted tubules that controls glucose reabsorption is sodium-glucose cotransporter 2 (SGLT2). An SGLT2 inhibitor reduces renal glucose reabsorption, which raises urine glucose excretion and lowers hyperglycemia.[5] For type 2 diabetes, empagliflozin is licensed as a monotherapy or an adjuvant treatment.[6, 7]

Vildagliptin inhibits dipeptidyl peptidase-4 (DPP-4) for an extended period of time by covalently binding to its catalytic site.[8] The effectiveness of these medications as a supplement to metformin monotherapy in the treatment of diabetes was assessed in recent research, with inconsistent findings.[9] In the long-term care of diabetes, vildagliptin and dapagliflozin are more effective than antidiabetic medications when added to metformin monotherapy, according to a recent network meta-analysis.[10]

Therefore, this trial was aimed to compare the outcome of empagliflozin versus vildagliptin in combination with metformin in individuals of type II diabetes mellitus. Through literature, it was observed that there is no difference between both drugs for change in glycemic level, and lipid profile, however both are effective in reducing glycemic index and lipid profile of diabetic individuals. But limited work has been done before in local population, which also showed insignificant results and there is a need to gather information about more appropriate drug to control glycemic level and maintain lipid profile to prevent cardiovascular events in diabetic individuals. Therefore, there is a need to conduct a study and get evidence for local population and that is why we have planned this study.

METHODOLOGY

After taking approval from institutional review board, this Randomized controlled trial was carried out at the Department of Medicine, AIMS, Muzaffarabad, AJK from 21 junuary, 2025 to 15 June, 2025.

By using openepi.com, sample size of 320 individuals; 160 in each group is calculated with 5% significance level, 80% power of study, and mean fasting blood sugar level i.e. 117±26 mg/dl with Empagliflozin and 126±31 mg/dl with Vildagliptin.[11] Individuals who fulfilled the following criteria were enrolled by using Non Probability, Consecutive sampling technique.

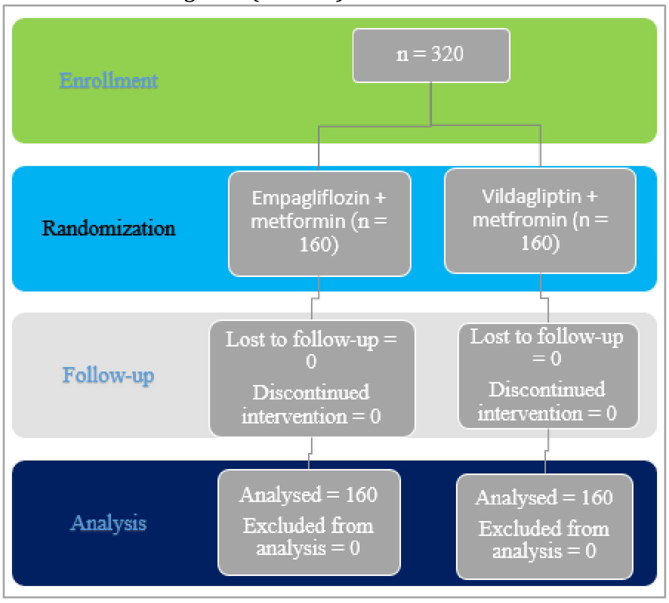
Inclusion Criteria: Individuals fall in age range 30-70 years, both genders, newly diagnosed cases of type II diabetes mellitus were enrolled. Type II diabetes mellitus: was defined as presence of HBA1c>6.5% for <3 months ago.

Exclusion Criteria: Individuals already taking trial treatment for last 3 months, chronic renal failure, hydronephrosis, or thyroid disease were excluded as they could cause bias in the study.

All the individuals were included from OPD. Informed consent was obtained. Demographics like name, age, gender, BMI, medical and personal history, any addiction, occupation, working hours, life style, dietary habits, were also noted. Then individuals were randomly divided in two groups by using lottery method. In Group-A, individuals were prescribed once daily oral empagliflozin plus metformin at the dose of 10/1000 mg. In Group-B, individuals were prescribed once daily oral vildagliptin plus metformin at the dose of 50/1000 mg. At baseline and after 12 weeks of follow-up, individuals were called in next OPD with 10-12 hours fasting. Blood sample to assess the HbA1c, fasting blood sugar and lipid profile. Pathology reports were assessed and values attained were recorded. HbA1c was recorded in terms of % changed from baseline until 12 week of therapy. Fasting blood glucose, total cholesterol and triglycerides were recorded in terms of mg/dl changed from baseline until 12 week of therapy. All this information was recorded in proforma.

Figure 1

Patient Flow Diagram (n= 320)



Data was analyzed in "Statistical Package for Social Sciences" v. 25.0. Normality was assessed by using Shapiro-Wilk test. Both groups will be compared for mean HbA1c level, fasting blood sugar level, and lipid profile by using "Independent Samples T-test" keeping P–value ≤ 0.05 as significant.

RESULTS

In this trial, we enrolled total 320 individuals and randomized them in two equal group. The mean age of individuals enrolled in Group-A was 56.16 ± 9.57 years as well as in Group-B was 57.86 ± 9.33 years. In Group-A, there were 94 (58.8%) men and 66 (41.3%) women. In Group-B, there were 79 (49.4%) men and 81 (50.6%) women. Their anthropometric parameter (BMI) and history is given in table below. Dyslipidemia was detected in 29 (18.1%) individuals in Group-A while in 45 (28.1%) individuals in Group-B. Mostly females were house wives (>30% cases) and among males, mostly were doing office jobs. In Group-A, about 112 (70.0%) were taking home made food, 39 (24.4%) were taking hostel meals, 9 (5.6%) were taking street food for >3 times per week while no individuals was taking fast food. In Group-B, about 115 (71.9%) were taking home made food, 27 (16.9%) were taking hostel meals, 12 (7.5%) were taking street food for >3 times per week while 6 (3.8%) individuals was taking fast food. Table-I

At baseline, the median HBA1c level was 8.00 (IQR: 1.80) % in Group-A that was reduced to 7.00 (IQR: 1.00) %, showing the median change in HbA1c level of 0.80 (IQR: 0.78) %. In Group-B, the median HBA1c level was 8.00 (IQR: 1.90) % that was reduced to 7.00 (IQR: 1.50) %, showing the median change in HbA1c level of 1.00 (IQR: 0.80) %. The difference in HbA1c level after 12 weeks was significantly lower in Group-A than Group-B. while median change was more achieve in Group-B, however the difference was insignificant (p>0.05). At baseline, the median fasting blood glucose level was 180.00 (IQR: 44.00) mg/dl in Group-A that was reduced to 150.00 (IQR: 20.00) mg/dl, showing the median change in fasting blood glucose level of 20.00 (IQR: 37.50) mg/dl. In Group-B, the median fasting blood glucose level was 180.00 (IQR: 120.00) mg/dl that was reduced to 160.00 (IQR: 65.00) mg/dl, showing the median change in fasting blood glucose level of 25.00 (IQR: 46.75) mg/dl. The difference in fasting blood glucose level after 12 weeks was significantly lower in Group-A than Group-B. while median change was more achieve in Group-B ($p>0.05$). Table-II

At baseline, the median Total cholesterol level was 194.00 (IQR: 45.00) mg/dl in Group-A that was reduced to 150.00 (IQR: 42.00) mg/dl, showing the median change in Total cholesterol level of 20.00 (IQR: 38.00) mg/dl. In Group-B, the median Total cholesterol level was 198.00 (IQR: 98.00) mg/dl that was reduced to 180.00 (IQR: 40.00) mg/dl, showing the median change in Total cholesterol level of 28.00 (IQR: 31.00) mg/dl. The difference in total cholesterol level after 12 weeks was significantly higher in Group-B than Group-A ($p<0.05$). At baseline, the median triglycerides level was 210.00 (IQR: 112.00) mg/dl in Group-A that was reduced to 180.00 (IQR: 49.00) mg/dl, showing the median change in triglycerides level of 28.00 (IQR: 40.00) mg/dl. In Group-B, the median triglycerides level was 210.00 (IQR: 112.00) mg/dl that was reduced to 180.00 (IQR: 50.00) mg/dl, showing the median change in triglycerides level of 29.00 (IQR: 79.00) mg/dl. The difference in triglycerides level after 12 weeks was insignificant in both groups ($p>0.05$). Table-III

Table I

Baseline parameters of individuals enrolled in the trial (n = 320)

	Trial group	
	Empagliflozin + metformin	**Vildagliptin + metformin**
n	160	160
Age (in years)	56.16 ± 9.57	57.86 ± 9.33
Gender		
Male	94 (58.8%)	79 (49.4%)
Female	66 (41.3%)	81 (50.6%)
BMI (kg/m²)	24.03 ± 2.66	22.73 ± 3.15
History of		
Smoking	61 (38.1%)	72 (45.0%)
Hypertension	84 (52.5%)	90 (56.3%)
Dyslipidemia	29 (18.1%)	45 (28.1%)
Family history of diabetes	46 (28.8%)	63 (39.4%)
Residence		
Rural	91 (56.9%)	100 (62.5%)
Urban	69 (43.1%)	60 (37.5%)
Occupation		
Office job	30 (18.75%)	14 (8.75%)
Business man	8 (5%)	5 (3.1%)
Driver	2 (1.25%)	12 (7.5%)
House wife	49 (30.6%)	64 (40%)
Farmer	6 (3.75%)	6 (3.75%)
Labour	2 (1.25%)	12 (7.5%)
Lady health visitor	1 (0.6%)	5 (3.1%)
Retired	30 (18.75%)	5 (3.1%)
Teacher / lecturer	32 (20%)	37 (23.1%)
Working hours	4.98 ± 3.50	4.86 ± 3.81
Diet pattern		
Home made	112 (70.0%)	115 (71.9%)
Street food	9 (5.6%)	12 (7.5%)
Fast food	0 (0.0%)	6 (3.8%)
Hostel	39 (24.4%)	27 (16.9%)

Table II

Change in glycemic index of diabetic individuals (n = 320)

	Trial group		p-value
	Empagliflozin + metformin	**Vildagliptin + metformin**	
n	160	160	
HbA1c at baseline	8.00 (IQR: 1.80)	8.00 (IQR: 1.90)	0.176
HbA1c after 12 weeks	7.00 (IQR: 1.00)	7.00 (IQR: 1.50)	0.040
Change in HBA1c level	0.80 (IQR: 0.78)	1.00 (IQR: 0.80)	0.772
Fasting blood glucose at baseline	180.00 (IQR: 44.00)	180.00 (IQR: 120.00)	0.026
Fasting blood glucose after 12 weeks	150.00 (IQR: 20.00)	160.00 (IQR: 65.00)	0.014
Change in Fasting blood glucose	20.00 (IQR: 37.50)	25.00 (IQR: 46.75)	0.020

Table II

Change in lipid profile of diabetic individuals (n = 320)

	Trial group		p-value
	Empagliflozin + metformin	**Vildagliptin + metformin**	
n	160	160	
Total cholesterol at baseline	194.00 (IQR: 45.00)	198.00 (IQR: 98.00)	0.067
Total cholesterol after 12 weeks	150.00 (IQR: 42.00)	180.00 (IQR: 40.00)	0.000
Change in Total cholesterol	20.00 (IQR: 38.00)	28.00 (IQR: 31.00)	0.096
Triglycerides at baseline	210.00 (IQR: 112.00)	210.00 (IQR: 112.00)	0.740
Triglycerides after 12 weeks	180.00 (IQR: 49.00)	180.00 (IQR: 50.00)	0.406
Change in Triglycerides	28.00 (IQR: 40.00)	29.00 (IQR: 79.00)	0.213

DISCUSSION

In this trial, we observed that the median change in HBA1c level in Group-A that was 0.80 (IQR: 0.78) % and in Group-B was 1.00 (IQR: 0.80) %. The median change in HBA1 was more achieve in Group-B, however the difference was insignificant ($p>0.05$). In Group-A, the median change in fasting blood glucose level of 20.00 (IQR: 37.50) vs. 25.00 (IQR: 46.75) mg/dl ($p>0.05$). The median change in total cholesterol level was 20.00 (IQR: 38.00) mg/dl vs. 28.00 (IQR: 31.00) mg/dl ($p<0.05$) and median change in triglycerides level was 28.00 (IQR: 40.00) vs. 29.00 (IQR: 79.00) mg/dl ($p>0.05$).

It has been reported in a study that with empagliflozin, mean HbA1c was changed from 9.42 ± 1.48 to 8.44 ± 1.08, mean fasting blood glucose from 166 ± 48 to 117 ± 26, total cholesterol from 225 ± 182 to 175 ± 56 and triglycerides from 207 ± 119 to 169 ± 77. Similarly with Vildagliptin, mean HbA1c was changed from 9.17 ± 1.36 to 8.35 ± 1.10, mean fasting blood glucose from 175 ± 60 to 126 ± 31, total cholesterol from 212 ± 83 to 190 ± 53 and triglycerides from 200 ± 66 to 161 ± 37. But the difference between both drugs for above stated outcomes was insignificant ($p>0.05$).[11]

HbA1c levels were significantly lowered with vildagliptin in a 52-week multicenter, randomised, active-controlled study.[12] Vildagliptin helped T2DM individuals reduce their blood sugar levels throughout the day in another research.[13] Moreover, empagliflozin demonstrated encouraging outcomes in lowering FBS and

HbA1c levels in a 12-week dose-ranging, double-blind, placebo-controlled study that involved individuals with poorly managed type 2 diabetes.[14] In a phase IIb trial, empagliflozin likewise showed comparable outcomes; study participants' FBS and HbA1c levels were seen to drop clinically significantly.[15]

In treatment-naive individuals with T2DM (n = 632), the largest clinical trial assessed vildagliptin monotherapy at doses of 50 mg once or twice daily and 100 mg once daily. The results showed that the 3 dose levels of vildagliptin resulted in a mean reduction in HbA1c levels of 0.5%, 0.5%, and 0.6%, respectively when compared with placebo (P<0.005). The reductions in fasting plasma glucose levels from baseline were 18, 14.4, and 14.4 mg/dl for the 3 respective dose levels (P = 0.021, 0.093, and 0.058, respectively, compared with placebo). Only the 50 mg twice-daily dose group showed a significant change in fasting lipid parameters, with a 4.5% reduction in total cholesterol levels (P = 0.048 compared with placebo).[16] Additionally, vildagliptin (50 mg BD) was found to be non-inferior to pioglitazone (30 mg OD) in lowering HbA1c, and more individuals with vildagliptin reached their target HbA1c compared to individuals on vildagliptin and glimepiride without causing hypoglycemia.[17]

Clinical trials have indicated that vildagliptin does not significantly impact weight and does not increase the risk of cardiovascular and cerebrovascular events.[17] The J-VICTORIA study observed that individuals with T2DM who received vildagliptin had significantly lower mean 24-hour blood glucose levels, Mean amplitude of glycemic excursion, the highest blood glucose level after supper, and hyperglycemia after breakfast compared to those taking sitagliptin. However, there were no notable differences in plasma levels of HbA1c, glycoalbumin, C-peptide immunoreactivity, and B-type natriuretic peptide, or plasminogen activator inhibitor-1 between individuals treated with vildagliptin and those treated with sitagliptin.[18]

In another randomized trial, Liu et al., observed that after week 24, changes in HbA1c were −1.01 ± 0.16% with empagliflozin. After week 24, the empagliflozin group showed significant reductions, than other drugs in fasting plasma glucose (P < 0.001) as well. Hypoglycemia was reported to be slightly, in 30.2% cases with empagliflozin. They came to the conclusion that adding empagliflozin for 24 weeks improved glycemic control and increased decreases in body weight and systolic blood pressure in Asian individuals with poorly managed diabetes who were using premixed insulin.[19]

The mean changes in mean HbA1c levels from baseline in both the groups (p=0.76) were in line with the study by Del Prato et al., that highlighted the combination of an SGLT2i (empagliflozin) and metformin to have better efficacy in long-term control of plasma glucose levels and mean HbA1c compared to the combination of a DPP-4i (vildagliptin) and metformin.[20] These observations were in contrast with meta-analyses by Wang et al., where the combination of metformin and vildagliptin was more effective compared to the combination of metformin and empagliflozin on the reduction of mean FPG and the mean HbA1c levels.[21] The mean change in mean fasting glucose levels from baseline in the both groups (p=0.068) was consistent with the study by Kumar.[22]

CONCLUSION

The change in glycemic level and lipid profile of diabetic individuals is similar whether vildagliptin is given or empagliflozin is given in combination with metformin. Now we have get the magnitudes suggesting both drugs to be equally efficient in controlling glycemic level as well as lipid profile of diabetics that can help to prevent cardiovascular events in diabetic individuals. However, vildagliptin performed somewhat better than empagliflozin.

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