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Original Research Article

Comparative Study of Change of HBA1C with Voglibose and Teneligliptin on Ongoing Metformin Monotherapy: A 12-Week Randomized Comparative Clinical Study

Manish Ranjan Shrivastava[1], Aman Kishor[2], Jwala Kumar[3*], Zaki Anwar Zaman[4]

[1,2,3,]Tutor, Department of Pharmacology, Bhagwan Mahavir Institute of Medical Science, Pawapuri, Nalanda, Bihar (India)

[4]Professor & Head of Department, Department of Pharmacology, Bhagwan Mahavir Institute of Medical Science, Pawapuri, Nalanda, Bihar (India)

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Corresponding author: Jwala Kumar
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Abstract

Background: One of the most challenging health problems of the 21st century is diabetes. 70% of all reviewed studies reported T2D prevalence of over 10% in Indigenous Peoples, who account for 6.2% of the global population. Dipeptidyl peptidase-4 (DPP-4) inhibitors are a relatively new class of antihyperglycemic agents that are now recommended as second- or first-line agents in the treatment of diabetes by guidelines like those of the American Diabetes Association (ADA) 2016, the American Association of Clinical Endocrinologists 2016, and the American College of Endocrinology 2016.

Aim and Objectives: The present study was aimed to find out the comparative ability to reduce glycosylated haemoglobin (HbA1c) with voglibose (one alpha glucosidase inhibitors) and teneligliptin (DPP 4 inhibitor).

Materials and methods: The present prospective cross-sectional study comprised eighty (80) patients with diabetes and on Metformin monotherapy with uncontrolled hyperglycaemia was a hospital based interventional study of both genders. Patients were divided into two groups for this clinical study in a prospective parallel group design. 40 patients were included in each group. Group A patients were on metformin + Voglibose combination therapy and Group B patients were on Metformin + teneligliptin combination therapy.

Results: The mean baseline HbA1c value was 8.35% in the Group A **(**Metformin + Voglibose) and 8.45 % in the Group B **(**Metformin + teneligliptin). There was no significant difference between mean HbA1c level between these two groups. The mean baseline FBS value was 162±26.4 mg/dl in group A and 167±25.7 mg/dl in group B. Mean serum LDL level was greater reduced (-21.4mg/dl) in teneligliptin, group B than voglibose, group A (-8.5mg/dl) [p value <0.05]. HDL level was slightly increased in both the groups and greater in teneligliptin, group B. Mean serumtriglycerides level was greater reduced (-20.2mg/dl) in teneligliptin, group B than voglibose, group A (-17.2mg/dl)but the differences are not significant.

Conclusion: The present study highlights the overall HbA1c lowering effect of Metformin + teneligliptin combination is more than Metformin+ voglibose. There is significant elevation of serum HDL- cholesterol as compared voglibose.

Keywords: Metformin, Teneligliptin, Voglibose.

Introduction

One of the most challenging health problems of the 21st century is diabetes. 70% of all reviewed studies reported T2D prevalence of over 10% in Indigenous Peoples, who account for 6.2% of the global population. Given that in 2022, only 1.52 million of the 8.75 million people with type 1 diabetes worldwide were under the age of 20. In a Senegalese study, 72% of diabetics had diabetic peripheral neuropathy. An adverse COVID-19 outcome is strongly correlated with diabetes. According to the IDF Diabetes Atlas, people with diabetes are at a significantly higher risk of being hospitalized and dying from COVID-19 infections than people without the condition**.** A systematic review was performed in 2022 to assess the likelihood of adverse COVID-19 outcomes in relation to glycemic control, blood glucose levels on admission to the hospital, and diabetes subtype. Adults with diabetes with a HbA1c level greater than or equal to 7% had a 35–40% increased risk of developing COVID-19 and a serious disease.[1]

Dipeptidyl peptidase-4 (DPP-4) inhibitors are a relatively new class of antihyperglycemic agents that are now recommended as second- or first-line agents in the treatment of diabetes by guidelines like those of the American Diabetes Association (ADA) 2016, the American Association of Clinical Endocrinologists 2016, and the American College of Endocrinology 2016.[2,3] DPP-4 inhibitors increase plasma concentrations of active glucagon-like peptide-1 by selectively inhibiting DPP-4 to control fasting plasma glucose (FPG) and postprandial plasma glucose (PPG) levels. DPP-4 inhibitors, unlike sulfonylureas, meglitinides, or insulin, are weight neutral and pose no risk of hypoglycemia. Teneligliptin is a brand-new DPP-4 inhibitor with a unique chemical structure characterized by five consecutive rings (J-shaped), which may explain its unique potency and half-life.[4] It was introduced in India in May 2015 and has a cost between a quarter and a fifth of that of other DPP-4 inhibitors (namely sitagliptin, vildagliptin, saxagliptin, and linagliptin). In a very short span of time (8–9 months), teneligliptin has become the most widely prescribed DPP-4 inhibitor in India.[5] For type 2 diabetes mellitus Metformin is the drug until it alone is able to keep glycemic levels within normal limits. However, even with metformin, many patients with T2DM remain inadequately managed, which results in progressively declining glycemic control.[6]

Aims and Objectives: In addition to metformin, the current study compared the ability of voglibose, an alpha glucosidase inhibitor, and teneligliptin, a DPP-4 inhibitor, to reduce glycosylated hemoglobin (HbA1c).

Materials and Methods

The present prospective cross-sectional study comprised eighty (80) patients with diabetes and on Metformin monotherapy with uncontrolled hyperglycaemia was a hospital based interventional study of both genders at Bhagwan Mahavir Institute of Medical Science, Pawapuri, Bihar, India, in the department of pharmacology, in collaboration with the department of medicine. The institutional ethical committee gave its clearance before the study could be carried out. The study was carried out between June 2022 and December 2022. All patients, attending General Medicine OPD were informed regarding the study, and their consent was obtained. Names, ages, genders, and other details about the patient were noted. Patients were divided into two groups for this clinical study in a prospective parallel group design. Group A patients were on

metformin + Voglibose combination therapy and Group B patients were on Metformin + teneligliptin combination therapy. The selection of patients in each group was done by randomization method. One group received teneligliptin 20mg twice daily in addition to metformin and the other group received Voglibose 0.3mg thrice daily in addition to metformin. HbA1c was assessed before introduction of additional drug and 12 weeks after starting additional drug.

Dosage Frequency

Voglibose: 0.3mg thrice daily. Mode of administration: Oral

Teneligliptin: One tablet to be taken orally once daily before breakfast every morning. In case patients were not controlled on 20mg Teneligliptin, dose may be up titrated to 40mg daily. The 40mg dose was administered as two 20 mg tablets taken orally once daily before breakfast every morning. Mode of administration: Oral.

Metformin, oral dosage form, 500mg tablet orally initially OD, then BD if not controlled. HbA1c, FPG and PPG levels was assessed at each visit. At 0, 6, and 12 weeks; tests evaluating liver functions, blood lipid profiles, blood amylase was performed at 0 and 12 weeks.

Inclusion Criteria

- Persons with diabetes and on Metformin monotherapy with uncontrolled hyperglycaemia.
- Ambulatory patients with Type 2 diabetes mellitus.
- Persons having inadequate glycaemic control with HbA1c above 6.5 % but < 10%.
- Patients who can be followed up and having PPBS above 200mg/dl.

Exclusion Criteria

- Type 1 Diabetes mellitus
- Non ambulatory patients with HbA1c above 10%.
- Known cases of diabetic nephropathy, diabetic ketoacidosis, diabetic coma, hyperglycemia hyperosmolar state, retinopathy, neuropathy.

Statistical analysis

Results thus obtained were subjected to statistical analysis with the help of Microsoft EXCEL 15 and SPSS Version 22.0 software. We performed Unpaired t test were used to perform the statistical analysis. The obtained data were then analyzed statistically. P values under 0.05 were deemed significant.

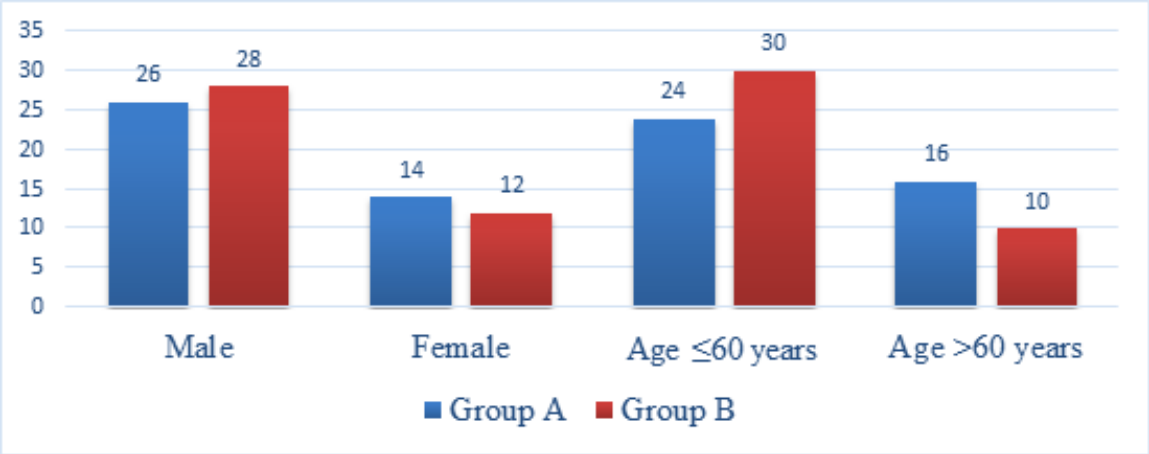
Results

The mean age of male patients was 52.5 ±10.6 (mean ± SD) years, whereas the mean age of female patients was 48.3± 12.7 (mean SD) years, respectively. Out of the entire patient population, 67.5% were males and 32.5% were females.

Table:1 shows the demographic, clinical, and laboratory characteristics of study participants

Patients' characteristics	Group A (metformin + Voglibose)	Group B (Metformin + teneligliptin)	P value
Number of patients	40	40	
Gender			
Male	26(65%)	28(70%)	
Female	14(35%)	12 (30%)	
Age			
≤60 years	24(60%)	30(75%)	
>60 years	16 (40%)	10 (25%)	
BMI (Mean±SD)	27.8±4.7 kg/m^2	26.8±4.9 kg/m^2	0.68
FBS (Mean±SD)	162±26.4 mg/dl	167±25.7 mg/dl	0.79

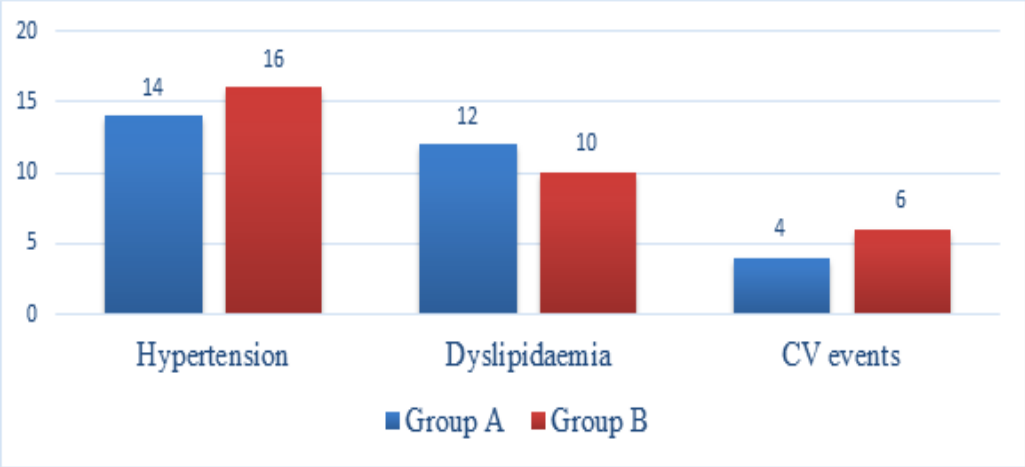
PPBS (Mean±SD)	252±33.7 mg/dl	242±34.5 mg/dl	0.53
HbA1c (Mean ±SD)	8.25±0.65	8.30±0.92	0.72
LDL-C	135±38.49 mg/dl	142±46.73 mg/dl	0.56
HDL	42.6±6.3 mg/dl	46.7±4.83 mg/dl	0.83
Triglycerides	195.1±32.7 mg/dl	190.4±26.5 mg/dl	0.72
Presence of co-morbidities			
Hypertension	14 (35%)	16(40%)	
Dyslipidaemia	12(30%)	10(25%)	
CV events	04(10%)	06(15%)	



Graph 1: Shows the demographic, clinical, and laboratory characteristics of study participants

Table 1, Graph I and II shows that there was no significant difference between the baseline characteristics of the two groups considering their age, sex, presence of co-morbidities, and fasting and postprandial blood sugar levels (FBS and PPBS levels). The glycaemic efficacy was assessed by analysing the mean changes in the values of FBG, PPBG, and HbA1c from the start of therapy to the end of the 12-week study period. The mean baseline HbA1c value was 8.35% in Group A (Metformin and Voglibose) and 8.45% in Group B (Metformin and Teneligliptin). There was no significant difference in mean HbA1c levels between these two groups. The mean baseline FBS value was 162±26.4 mg/dl in group A and 167±25.7 mg/dl in group B.

Graph 1 shows the mean level of glycosylated haemoglobin (HbA1c) before starting additional drugs.



Graph 2: Presence of co-morbidities

Table 2: shows the changes in glycemic parameters after completion of 12 weeks of therapy with metformin and voglibose vs. metformin and teneligliptin.

Parameters	Treatment Group	Baseline values	After completion of 12 weeks therapy	Changes from baseline	P value
FBS (Mean±SD) (In mg/dl)	A	162±26.4	146.9±25.3	-15.1	<0.05
	B	167±25.7	148.6±26.2	-18.4	
PPBS (Mean±SD) (In mg/dl)	A	252±33.7	206.7±32.6	-45.3	<0.05
	B	242±34.5	192.5±33.9	-49.5	
HbA1c(Mean±SD) (In %)	A	8.25±0.65	7.08±0.89	-1.17	<0.05
	B	8.30±0.92	6.90±0.92	-1.40	
LDL-C (In mg/dl)	A	135±38.49	126.5±34.9	-8.5	<0.05
	B	142±46.73	120.6±38.5	-21.4	
HDL (In mg/dl)	A	42.6±6.3	46.8±4.5	+4.2	>0.05
	B	46.7±4.83	52.9±5.3	+6.2	
Triglycerides (In mg/dl)	A	195.1±32.7	177.8±36.5	-17.2	>0.05
	B	190.4±26.5	170.2±30.6	-20.2	

At the end of 12 weeks or 3 months of Metformin + Voglibose therapy, mean HbA1c, FBG, and PPG were significantly reduced by 1.17%, 15.1 mg/dL, and 45.3 mg/dL, respectively, whereas with Metformin + Teneligliptin therapy, mean HbA1c, FBG, and PPG were significantly reduced by 1.40%, 18.4 mg/dL, and 49.5 mg/dL, respectively (Table 2).

So, after completion of 12 weeks of therapy with an additional drug, people receiving teneligliptin had a significantly lower level of HbA1c than people receiving voglibose. It was seen that with both drugs, the level of HbA1c decreased. It was further noticed that the change in HbA1c with voglibose was less than the change in HbA1c with teneligliptin. This difference was also found to be statistically significant at p <0.05.

Graph 2 shows the mean level of glycosylated haemoglobin (HbA1c) after completion of 12 weeks of therapy with additional drugs.

The mean serum LDL level was reduced more (-21.4 mg/dl) in teneligliptin, group B, than in voglibose, group A (-8.5 mg/dl) [p value 0.05]. HDL levels were slightly increased in both groups and greater in teneligliptin, group B. The mean serum

triglyceride level was reduced more (-20.2 mg/dl) in teneligliptin, group B, than in voglibose, group A (-17.2 mg/dl), but the differences are not significant (Table 2).

Discussion

Glycosylated hemoglobin (HbA1c) gives an overall picture of glycemic control over the past three months (12 weeks). The target HbA1c should be within 7%. Several studies have been done in different regions of the world comparing the efficacy of different DPP4 inhibitors with voglibose. Teneligliptin and voglibose are the most affordable and effective DPP-4 inhibitors and are widely used in India, but there hasn't been a head-to-head comparison of their efficacy.

Effects of metformin plus voglibose vs. metformin plus teneligliptin therapy on glycosylated hemoglobin (HbA1c)

In a study by Dabhi AS et al. [7], it was found that the mean change of HbA1c was -0.38 ±0.04% with voglibose 0.2mg TDS dosage, as compared to -0.95±0.04% in the group treated with vildagliptin 50mg BD. Moreover, a much lower percentage of patients (24% compared with 51%) in the voglibose group than in the vildagliptin group achieved an endpoint HbA1c of 6.5%.

Another study by Iwamoto Y et al. also finds the superiority of vildagliptin over voglibose in reducing HbA1c.[8] Similar to the previous study, another one by Matsushima Y et al. highlights sitagliptin's superiority over voglibose.[9]

In the present study, at the end of 12 weeks or 3 months of Metformin + Voglibose therapy, mean HbA1c, FBG, and PPG were significantly reduced by 1.17%, 15.1 mg/dL, and 45.3 mg/dL, respectively, whereas with Metformin + Teneligliptin therapy, mean HbA1c, FBG, and PPG were significantly reduced by 1.40%, 18.4 mg/dL, and 49.5 mg/dL, respectively. So, after completion of 12 weeks of therapy with an additional drug, people receiving teneligliptin had a significantly lower level of HbA1c than people receiving voglibose.

Due to the high cost of DPP4 inhibitors, poor patients are often unable to continue these for a long time. Unlike other DPP4 inhibitors, teneligliptin has a much lower cost. So, in rural India, its use is popular considering its high compliance among poor patients. Teneligliptin, which is classified as a peptidomimetic, has a unique structure with five consecutive rings.[10] Based on the results of a few head-to-head trials or meta-analyses comparing the efficacy of DPP-4 inhibitors, there is a general consensus that the HbA1c-lowering effects of gliptins are broadly similar.[11,12] Voglibose belongs to a class of comparative alpha glucosidase inhibitors and causes reversible inhibition of membrane-bound intestines alpha glucosidase, which hydrolyzes oligosaccharides and disaccharides to glucose and other monosaccharides in the brush border of the small intestine. So voglibose delays the absorption and digestion of dietary polysaccharides by reversibly inhibiting carbohydrate digestive enzymes like sucrose, maltose, zomaltose, etc., ultimately resulting in a reduction of PPBS as well as HbA1c. Teneligliptin is able to lower the PPBS as well as HbA1c significantly in 4 weeks compared to a placebo. Teneligliptin 20mg OD is found to be more potent than voglibose 0.2mg TDS.[13]

Effects of Metformin and Voglibose vs. Metformin and Teneligliptin Therapy on Lipid Profiles

Meta-analyses suggested a potential beneficial effect of DPP-4 inhibitors on cholesterol, which could contribute to a reduction in cardiovascular risk.[14] GLP-1 inhibits the secretion of gastric lipase and reduces intestinal triglyceride absorption and apo B and apo A-IV production, and insulin suppresses lipolysis in adipose tissue, resulting in a reduction of the plasma free fatty acid levels; therefore, the study

speculated that the reduction in triglyceride and free fatty acid levels could be a consequence of the elevation of active GLP-1 and insulin levels.[15]

In the present study, the mean serum LDL level was reduced more (-21.4 mg/dl) in Metformin + teneligliptin therapy than in Metformin + voglibose therapy (-8.5 mg/dl) [p value <0.05]. HDL level was slightly increased in both groups and greater in Metformin + Telegiliptin therapy. The mean serum triglyceride level was greater and reduced (-20.2 mg/dl) in Metformin + Teneligliptin therapy than in Metformin + Voglibose therapy (-17.2 mg/dl). [16,17]

Limitations of study

The limitations of the present study are that the number of subjects is small, and the study duration is short.

Conclusion

Many new drugs have been developed in the DPP-4 inhibitor class, and their efficacy has been studied in detail. But a head-to-head study comparing the efficacy of the cheapest and most widely used DPP-4 inhibitor in India, i.e., teneligliptin versus voglibose, is lacking. The present study highlights the fact that the overall HbA1c lowering effect of teneligliptin 20mg BD is greater than that of voglibose 0.3 mg TDS. There is a significant elevation of serum HDL-cholesterol and teneligliptin as compared to voglibose. But both drugs lower PPBS as well as HbA1c levels significantly over metformin monotherapy.

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