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THE EFFECT OF TENELIGLIPTIN AS ADD ON THERAPY TO CONVENTIONAL METFORMIN THERAPY IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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ABSTRACT

Introduction A number of oral hypoglycaemic agents are available among which metformin and sulfonylureas are the commonly prescribed drugs. Dipeptidyl peptidase inhibitors are a relatively new class of drugs. This study was carried out to examine the efficacy and safety of teneligliptin as an add on drug to metformin in patients with Type 2 Diabetes Mellitus. **Materials and Methods** The study was conducted among 100 patients with Type 2 Diabetes Mellitus who were newly diagnosed and never on drugs. They were divided into two groups of 50 each and were prescribed either Metformin alone or a combination of Metformin and Tenegliptin for 3 months. All the study participants were subjected to laboratory investigations to check for their glycemic parameters, lipid profile and hepatic profile **Result** The fasting blood sugars, post prandial blood sugars and HbA1c reduced over a period of time in both the groups. It was seen that combination of Metformin and Tenegliptin were much effective in reduction of FBS, PPBS and HbA1c over a period of time when compared to prescription of Metformin alone. There was a reduction in triglyceride values between baseline and 12 weeks in both the groups. But there was no significant reduction in other parameters. **Conclusion** A combination of Metformin and Tenegliptin was much more effective in reduction of blood sugars when compared to Metformin alone.

KEYWORDS : Tenegliptin, Metformin, Glycemic control

INTRODUCTION

Diabetes Mellitus is a chronic metabolic non communicable disease and has attained a position of one of the largest global health emergencies over a period of time[1,2]. It is characterized by hyperglycemia resulting from decreased insulin secretion by beta cells of pancreas or increased insulin resistance[3]. According to the International Diabetes Federation report, 2010, an estimated 50 million people were living with diabetes, and it is projected to increase to 87 million by the year 2030. India may be one of the fastest-growing countries with T2DM[4-6].

Diabetes Mellitus requires lifelong care which includes patient education, prevention of complications and support[7,8]. Even though there are a number of oral hypoglycaemic agents available, it is difficult in some of the patients to maintain a good glycemic control because of non compliance to drugs which may be secondary to certain side effects associated with them[9,10]. The most commonly prescribed oral hypoglycaemic agents are metformin and sulfonylureas[11,12].

Dipeptidyl peptidase inhibitors are a relatively new class of drugs that are recommended as second or first line agents in treatment of diabetes as per the guidelines of American Diabetic Association (ADA) 2016 and American College of Endocrinology[13-15].

Teneligliptin is a dipeptidyl peptidase inhibitor which is a new and relatively economic drug. It works by increasing levels of active glucagon-like peptide-1 (GLP-1), thereby promoting insulin secretion and improving beta-cells sensitivity to glucose[16,17]. It has a unique chemical structure which is characterized by five consecutive rings (J-shaped), which might account for its unique potency and half-life time[18].

Metformin mainly decreases Fasting Plasma Glucose (FPG), while DPP-4 mainly inhibits Post Prandial Glucose (PPG) according to certain studies[19]. Therefore, DPP-4 inhibitors could be more efficient in Indian patients consuming a traditional Indian diet. Thus the study was carried out to examine the efficacy and safety of teneligliptin as an add on drug to metformin in patients with Type 2 Diabetes Mellitus.

MATERIALS AND METHODS

The study was conducted among 100 patients with Type 2 Diabetes Mellitus who attended outpatient department of General Medicine at Chamarajanagar Institute of Medical Sciences, Karnataka. The patients who were newly diagnosed to be having Type 2 Diabetes Mellitus and never on drugs were randomly divided into two groups of 50 each and were prescribed either Metformin alone or a combination of Metformin and Tenegliptin for 3 months. The study was conducted between May 2020 and May 2022. Permission from the Institutional Ethics Committee was obtained before starting the study. The study participants and their accompanying family members were interviewed by semi structured questionnaire.

Inclusion Criteria:

All patients who were diagnosed as having Type 2 Diabetes Mellitus, not on any hypoglycaemic agents before, and aged between 18 and 65 years were included. These patients were put on drugs after making sure that there was no glycemic control in them in spite of life style modifications.

Exclusion Criteria:

Patients with Type 1 Diabetes Mellitus, Pregnant and Lactating Mothers, Patients with Diabetic Complications and patients on steroid treatment were excluded. Patients with chronic kidney disease, liver failure, stroke, severe infection, coronary heart disease and hypertensive emergencies were also excluded.

After obtaining written informed consent the patients in one group were prescribed Tablet Tenegliptin 20 mg which was taken orally early in the morning once daily before breakfast. If glycemic control was not achieved, then two tablets were prescribed. The other group of patients were prescribed Tab Metformin 500 mg orally after breakfast as one tablet along with Tab Tenegliptin 20mg orally before breakfast. If glycemic control was not achieved, then the dose of tenegliptin was increased by another 20 mg orally.

Fasting Plasma Glucose, Post prandial Plasma Glucose and HbA1c were assessed at each visit. Blood investigations to

assess liver function test, Lipid profile and Serum Amylase were performed at 0, 6 and 12 weeks.

Statistical Analysis:

The data was entered in Microsoft Office Excel 2007 and IBM SPSS version 21 was used for analysis. Chisquare test, Unpaired Student t test and Paired T Test were used to find the statistical significance. P value less than 0.05 were considered statistically significant.

RESULTS:

There were a total of 50 participants each in Group A (Metformin alone) and Group B (Metformin + Tenegliptin). In Group A the male: female ratio was 2.12:1 and in Group B the ratio was 2.84:1. There was no statistically significant difference between the gender distribution among the groups. Most of the study participants in Group A and B belonged to 41 – 60 years age group and accounted for 58% and 74% respectively. There was statistically significant difference between the age groups among the study population. 74% of the study population in Group A and 84% in Group B had a normal BMI. 6% of them in Group A and 2% in Group B were obese. There was no statistically significant difference in BMI among the groups. (Table 1)

All the study participants in Group A and Group B were subjected to laboratory investigations to check for their glycemic parameters, lipid profile and hepatic profile. There was no statistically significant difference in the laboratory parameters between the groups.(Table 2)

The fasting blood sugars, post prandial blood sugars and HbA1c reduced over a period of time in both the groups. There was a significant difference between Group A and Group B with respect to FBS at 6 weeks and 12 weeks. Similar difference was observed in HbA1c. However there was no statistically significant difference between Group A and Group B at 6 weeks with respect to PPBS even though there was a reduction from baseline in both the groups. But there was significant difference between Group A and Group B at 12 weeks with respect to PPBS. It was seen that combination of Metformin and Tenegliptin were much effective in reduction of FBS, PPBS and HbA1c over a period of time when compared to prescription of Metformin alone. (Table 3)

There was significant difference between baseline FBS and FBS at 6 weeks, between baseline FBS and FBS at 12 weeks in Group A and B. In Group A there was no significant difference in FBS between 6 weeks and 12 weeks. But in Group B there was significant difference in FBS between 6 weeks and 12 weeks. With regards to PPBS and HbA1c there was difference between baseline values and 6 weeks, between baseline and 12 weeks, between 6 weeks and 12 weeks.(Table 4). There was significant reduction in blood sugars over a period of time and this reduction was much higher in Group B than Group A. (Table 3)

- The lipid profile values and liver function test results over a period of time are tabulated in Table 5.
- There was a reduction in triglyceride values between baseline and 12 weeks in both the groups. But there was no significant reduction in other parameters. (Table 6).

DISCUSSION:

There is a need to find an effective add on therapy to metformin besides standard therapy to prevent the uncontrolled diabetes. This therapy should not only enhance the efficacy of treatment but at the same time, reduce the economic burden on the patient. The American Diabetic Association recommend life style modification as the first line and mainstay of treatment for Type 2 Diabetes Mellitus. Oral Metformin tablets is the preferred initial oral hypoglycaemic agent in most of the cases. There is no consensus as to which class of drugs can be used in dual and triple therapy[10-12,20]. This study was done to assess the efficacy of teneligliptin and metformin as a combination when compared to standard metformin monotherapy as initial pharmacotherapeutic option for Type 2 Diabetes Mellitus.

Metformin is widely used in clinical practice even though they are known for some of its common side effects like gastro intestinal intolerance and lactic acidosis. So increasing the dosage of metformin will only increase the incidence of side effects in the patients. Studies have shown that tenegliptin is safe and efficacious in the treatment of Type 2 Diabetes Mellitus[21,22]. It improves the glucose intolerance and synergistically increased plasma GLP-1 levels in Zucker diabetic fatty rats suggesting that teneligliptin might help in diabetes and obesity[23,24]. The present study also suggested that the HbA1c of the study population decreased significantly over a period of time and at the end of 12 weeks, the group which received metformin and tenegliptin combination had their mean HbA1c levels below 7%.

The fasting and post prandial blood sugars also reduced significantly in both the groups but more so in Group B. The study conducted by Vijay Raghavan et al[25] in West Bengal in 2017 showed that FBS and PPBS were reduced in the group which took metformin alone and also in the group which was prescribed metformin with tenegliptin. But the group which received the combination showed a higher degree of reduction of Post prandial blood sugars.

The present study also showed that there was significant reduction in triglyceride levels, more so in Group B when compared to Group A. Lipid profile is considered as an important risk factor for cardiovascular disease in diabetes mellitus. Metaanalyses points towards a potential benefit of DPP-4 inhibitors on lipid profile and this could have an influence on the reduction of cardiovascular risk[26,27]. 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[25].

Limitations:

The study involved a small number of study participants. The duration of the study was small. The second group received both metformin and tenegliptin, so the effect that is seen on the patients could not be really concluded as to which drug has really caused it.

CONCLUSION:

Teneligliptin, a DPP4 inhibitor reduced HbA1C significantly compared with monotherapy of metformin alone. It also significantly reduced FBS and PPBS as compared with metformin. The serum triglyceride levels also reduced significantly. So, teneligliptin improves serum lipid profile which is very important in T2DM patients with dyslipidemia. Therefore tenegliptin can be considered as a good additive to metformin in the treatment of Type 2 Diabetes Mellitus.

Table 1: Baseline Characteristics Of The Study Population

SNO.	Baseline Characteristics	GROUP A (Metformin alone)	GROUP B (Metformin+ Tenegliptin)	CHISQUARE VALUE	P VALUE
1	No. of Participants	50 (50%)	50 (50%)		-------
2	Gender				
	Male	34 (68%)	37 (74%)	0.4371	0.5085
	Female	16 (32%)	13 (26%)		
3	Age				
	18 – 40 Years	12 (24%)	8 (16%)	2.9126	0.2331
	41 – 60 Years	29 (58%)	37 (74%)		
	61 – 65 Years	9 (18%)	5 (10%)		

4	BMI				
	≤18.5	2 (4%)	1 (2%)	1.9355	0.5859
	18.5 – 24.99	37 (74%)	42 (84%)		
	25 – 29.99	8 (16%)	6 (12%)		
	≥30	3 (6%)	1 (2%)		

Table 2: Baseline Laboratory Parameters In The Study Population

SNO.	LABORATORY PARAMETERS	GROUP A (Metformin alone)	GROUP B (Metformin + Tenegliptin)	T VALUE	P VALUE
1	FBS	165.86 ± 16.74	167.3 ± 16.03	0.4393	0.6614
2	PPBS	251.58 ± 31.56	246.66 ± 27.63	0.8294	0.4089
3	HbA1c	7.81 ± 1.29	8.05 ± 1.49	0.8611	0.3913
4	LDL	142.58 ± 16.12	144.78 ± 21.00	0.5876	0.5581
5	HDL	43.92 ± 7.79	45.28 ± 8.00	0.8612	0.3912
6	TGL	187.48 ± 12.65	191.26 ± 14.01	1.4160	0.1599
7	AMYLASE	81.38 ± 8.48	82.92 ± 7.90	0.9396	0.3497
8	SGOT	39.06 ± 7.60	41.8 ± 6.62	1.9223	0.0575
9	SGPT	40.04 ± 7.69	42.04 ± 6.35	1.4181	0.1593
10	ALP	62.34 ± 6.65	63.94 ± 5.98	1.2650	0.2089

Table 3: Difference In Glycemic Parameters Between The Two Groups

SNO.	LABORATORY PARAMETERS	GROUPS	MEAN ± SD	AT 6 WEEKS	AT 12 WEEKS
1	FBS	GROUP A	165.86 ± 16.74	137.16 ± 13.92	134.1 ± 15.27
		GROUP B	167.3 ± 16.03	120.5 ± 11.56	109.04 ± 15.44
		T VALUE	0.4392	6.5088	8.1577
		P VALUE	0.6615	<0.0001*	<0.0001*
2	PPBS	GROUP A	251.58 ± 31.56	198.46 ± 36.51	178.4 ± 38.90
		GROUP B	246.66 ± 27.63	185.52 ± 38.50	163.56 ± 29.46
		T VALUE	0.8293	1.7242	2.1501
		P VALUE	0.4089	0.0878	0.0340*
3	HbA1c	GROUP A	7.81 ± 1.29	7.36 ± 0.66	7.02 ± 0.46
		GROUP B	8.05 ± 1.49	7.01 ± 0.26	6.78 ± 0.31
		T VALUE	0.8611	3.4889	3.0594
		P VALUE	0.3913	0.0007*	0.0029*

Table 4: Difference In Glycemic Parameters Over A Period Of Time

SNO.	LABORATORY PARAMETERS	GROUPS	BETWEEN BASELINE AND 6 WEEKS	BETWEEN BASELINE AND 12 WEEKS	BETWEEN 6 WEEKS AND 12 WEEKS
1	FBS	GROUP A	<0.0001*	<0.0001*	0.2976
		GROUP B	<0.0001*	<0.0001*	<0.0001*
2	PPBS	GROUP A	<0.0001*	<0.0001*	0.0092*
		GROUP B	<0.0001*	<0.0001*	0.0018*
3	HbA1c	GROUP A	0.0002*	<0.0001*	<0.0001*
		GROUP B	<0.0001*	<0.0001*	0.0002*

Table 5: Laboratory Parameters Over A Period Of Time

SNO.	LABORATORY PARAMETERS	GROUP A (BASELINE)	GROUP A (AFTER 12 WEEKS)	GROUP B (BASELINE)	GROUP B (AFTER 12 WEEKS)
1	LDL	142.58 ± 16.12	137.28 ± 16.50	144.78 ± 21.00	133.88 ± 15.04
2	HDL	43.92 ± 7.79	41.74 ± 5.73	45.28 ± 8.00	44.2 ± 6.68
3	TGL	187.48 ± 12.65	176.36 ± 17.07	191.26 ± 14.01	160.56 ± 16.05
4	AMYLASE	81.38 ± 8.48	79.94 ± 8.45	82.92 ± 7.90	80.06 ± 8.40
5	SGOT	39.06 ± 7.60	38.02 ± 7.50	41.8 ± 6.62	40.24 ± 5.94
6	SGPT	40.04 ± 7.69	38.9 ± 6.30	42.04 ± 6.35	42.34 ± 6.09
7	ALP	62.34 ± 6.65	61.52 ± 6.63	63.94 ± 5.98	60.46 ± 7.38

Table 6: Difference In Laboratory Parameters Over A Period Of Time

SNO.	LABORATORY PARAMETERS	GROUP A BASELINE Vs 12 WEEKS	GROUP B BASELINE Vs 12 WEEKS
1	LDL	0.1075	0.0036*
2	HDL	0.1144	0.4659
3	TGL	0.0004*	<0.0001*
4	AMYLASE	0.3971	0.0826
5	SGOT	0.4931	0.2183
6	SGPT	0.4198	0.5754
7	ALP	0.5389	0.05111

REFERENCES:

1. International Diabetes Federation. IDF Diabetes Atlas. 9th ed. Brussels, Belgium: International Diabetes Federation; 2019.
2. World Health Organization. The top 10 causes of death. Available from: http://www.who.int/en/news-room/fact-sheets/detail/the-top-10-causes-of-death . Last accessed on 3rd August 2022.
3. Nikhra V. Exploring complexities of T2DM: Insulin signaling, resistance and deficiency, metabolic links, sexual dimorphism and endocrine disruptors. Res Med Eng Sci 2018;5:1-10
4. Ramachandran A, Das AK, Joshi SR, Yajnik CS, Shah S, Kumar KM. Current status of diabetes in India and need for novel therapeutic agents. J Assoc Physicians India 2010;58:7-9.
5. Aschner P. New IDF clinical practice recommendations for managing Type 2 diabetes in primary care. Diabetes Res Clin Pract 2017;132:169-70.
6. Gupta CN, Raghavan V, Sen S, Kothari S. Role of teneligliptin in rural India as add-on third drug in patients with Type 2 diabetes mellitus. Int J Adv Med 2017;4:401-5.
7. Riddle MC, Bakris G, Blonde L, Boulton AJ, D'alessio D, De Groot M, et al. Standard medical care in diabetes 2018. Diabetes Care 2018;41:S119-25.
8. 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.
9. Feingold KR, Anawalt B, Boyce A, Chrousos G, Dungan K, Grossman A, et al. Oral and Injectable (Non-insulin) Pharmacological Agents for Type 2 Diabetes. South Dartmouth, MA: MDText.com, Inc.; 2019.
10. Wang CY, Neil DL, Home P 2020 vision-an overview of prospects for diabetes management and prevention in the next decade. Diabetes Res Clin Pract 2018;143:101-12.
11. Indian Council of Medical Research. ICMR Guidelines for Management of Type 2 Diabetes. Pharmacological Treatment For Diabetes. New Delhi: Indian Council of Medical Research; 2005. p. 16-31.
12. Snehalatha C, Priscilla S, Nanditha A, Arun R, Satheesh K, Ramachandran A, et al. Metformin in prevention of Type 2 diabetes. J Assoc Physicians India 2018;66:60-3.
13. American Diabetes Association. Standards of medical care in diabetes-2016. Diabetes Care. 2016;39 (Suppl 1):S1-S106.
14. 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.
15. Ghosh S, Trivedi S, Sanyal D, Modi KD, Kharb S. Teneligliptin real-world efficacy assessment of type 2 diabetes mellitus patients in India (TREAT-INDIA study). Diabetes, Metabolic Syndrome Obesity: Targets Therapy. 2016;9:347.
16. 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.
17. Kim Y, Kang ES, Jang HC, Kim DJ, Oh T, Kim ES, et al. Teneligliptin versus sitagliptin in Korean patients with Type 2 diabetes inadequately controlled with metformin and glimepiride: A randomized, doubleblind, non-inferiority trial. Diabetes Obes Metab 2018;1-9.
18. Scott LJ. Teneligliptin: a review in type 2 diabetes. Clin Drug Investig. 2015;35(11):765-72.
19. Doupis J, Veves A. DPP4 inhibitors: a new approach in diabetes treatment. Adv Ther. 2008;25:627-43.
20. Joshi S, Jadhav V, Kadam V. Exotic fruits and vegetable food as nutritional supplement for diabetes, obesity and metabolic diseases. Int J Curr Pharm Res 2018;10:51-5.
21. Li X, Huang X, Bai C, Qin D, Cao S, Mei Q, et al. Efficacy and safety of teneligliptin in patients with Type 2 diabetes mellitus: A systematic review and meta-analysis of randomized controlled trials. Front Pharmacol 2018;9:449.
22. Bajaj S. RSSDI clinical practice recommendations for the management of Type 2 diabetes mellitus 2017. Int J Diabetes Dev Ctries 2018;38:1-15.
23. Takeda K, Sawazaki H, Takahashi H, Yeh YS, Jheng HF, Nomura W, et al. The dipeptidyl peptidase-4 (DPP-4) inhibitor teneligliptin enhances brown adipose tissue function, thereby preventing obesity in mice. FEBS Open Bio 2018;8:1782-93.
24. Oguma T, Kuriyama C, Nakayama K, Matsushita Y, Yoshida K, Kiuchi S, et al. The effect of combined treatment with canagliflozin and teneligliptin on glucose intolerance in zucker diabetic fatty rats. J Pharmacol Sci 2015;127:456-61
25. Raghavan V, Lahiri A, Akul S K, Goswami U, Gupta C N, Sen S. Effect of teneligliptin vs metformin on glycemic control in Indian patients with newly-diagnosed, drug-naïve type 2 diabetes mellitus: a 12-week randomized comparative clinical study. Int J Adv Med 2019;6(2):481-88.
26. Monami M, Lamanna C, Desideri CM, Mannucci E. DPP-4 inhibitors and lipids: systematic review and meta-analysis. Adv Ther. 2012;29:14-25
27. Hsieh J, Longuet C, Baker CL, Qin B, Federico LM, Drucker DJ et al. The glucagon-like peptide 1 receptor is essential for postprandial lipoprotein synthesis and secretion in hamsters and mice. Diabetologia. 2010;53:552-61.