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ORIGINAL ARTICLE

Comparison of Efficacy and Safety of Metformin Vs Teneligliptin as Add on to Metformin in Type 2 Diabetes Mellitus at a Tertiary Care Hospital

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ABSTRACT

The present research was a randomized open label prospective cross sectional study which was conducted at Diabetic clinic, General Medicine Department, Sree Balaji Medical College and Hospital during the period of April 2019 to September 2019. The study duration was 24 weeks (6 months). Total 100 study participants of both sexes with T2DM were included as per inclusion criteria in the study. They were randomized into two different groups. Group 1 – Metformin 850mg BD treatment group consisting of 50 patients; Group 2– Teneligliptin 20mg OD+ Metformin 500mg BD also consisting of 50 patients and only 43 patients in high dose Metformin group and 48 patients in Teneligliptin+ Metformin group were completed the study at the end of study period (24 weeks). Initial lab parameters have been done for all study participants and treatment was initiated. All data collected were analyzed using appropriate statistical methods and evaluated. The primary efficacy endpoint was mean change in HbA1c from baseline to till 24 weeks was significant with Teneligliptin 20mg OD + Metformin 500mg BD group compared to Metformin 850mg BD group. Decreased mean change in Glycosylated hemoglobin was reported in both the study groups; However the Teneligliptin 20mg OD + Metformin 500mg BD group had higher improvement than Metformin 850mg BD group in T2DM patients. As of quality of life, both patient and clinician felt significant improvement for Teneligliptin plus Metformin therapy when compared to high dose Metformin monotherapy which is similar with preceding studies. The secondary efficacy endpoint was mean change in Fasting blood sugar (FBS), Postprandial blood sugar (PPBS) from starting of study to till end of 24 weeks of study period was found to have significant improvement with Teneligliptin 20mg OD plus Metformin 500mg BD group when compared to Metformin 850mg BD group. The secondary safety endpoint profile of both study groups showed that there was no non-compliance incidence due to adverse event. But the number of adverse effects (events) was higher in metformin 850mg BD group. Both the study groups reported gastrointestinal disturbances as the common symptoms. In this study DPP-4 inhibitor Teneligliptin 20mg OD as add on to Metformin 500mg BD was found to be safe and efficacious when compared to high dose Metformin 850mg BD in whom glycaemic levels were uncontrolled previously.

Keywords: Metformin, Teneligliptin, Type 2 Diabetes, DPP-4 inhibitor

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INTRODUCTION

Diabetes is a most prevalent non communicable disease and has reached to a level of epidemic stage in most of the countries. Globally, 415 million people are under treatment for diabetes and a cardiovascular complication due to this is the leading cause of mortality, followed by cancer. It is the major cause of kidney failure, blindness, stroke, heart attacks and lower limb amputation. WHO estimates that diabetes was the seventh principal cause of mortality in 2016 Type 2 Diabetes mellitus (T2DM) a major lifestyle disease is undoubtedly the most challenging public health problem of 21st century and it is the leading cause of morbidity and mortality worldwide and a major problem in India [1, 2]. The number of persons

with type 2 Diabetes Mellitus is rapidly increasing worldwide, especially in the Asian countries, because of aging population and changes in dietary habits [5]. As per the Diabetes Atlas 2006 by the International Diabetes Federation, the number of persons with diabetes mellitus in India currently around 40.9 million is estimated to rise to 69.9 million by 2025 unless urgent preventive steps are taken [3]. Metformin an oral anti hyperglycemic drug used in the treatment of T2DM has vital role in lowering basal, postprandial plasma g
that a reduction of 1% HbA1C level will reduce the risk of micro and macro vascular complications associated with Type 2 Diabetes Mellitus [4,5]. Hence this study was undertaken to compare the effectiveness and safety of Teneligliptin with metformin combination therapy against high dose metformin monotherapy in type 2 diabetes mellitus patients.

MATERIAL AND METHODS

Study Design:
Prospective, randomized, open labelled, cross sectional study comparing the effects of Metformin 850mg BD versus Teneligliptin 20mg OD with Metformin 500mg BD in patients suffering with T2DM.

Study Venue:
This research study was conducted in patients suffering from T2DM, attending the outpatient General Medicine Department in Diabetic clinic of Sree Balaji Medical College and Hospital, Chromepet, Chennai.

Study Period:
The study period was from April 2019 – September 2019.

Method of collection of data:

Sample Size:
Total sample size consisted of 100 patients

Duration of Study:
The total duration of study was 24 weeks
Study Groups: 2 Arms

- Tablet. Metformin 850 mg BD daily.
- Tablet. Metformin 500mg BD + Tablet. Teneligliptin 20 mg OD daily.

Study Procedure**:**
This study "To compare the Effectiveness and Safety of Metformin 850mg BD versus Teneligliptin 20mg OD with Metformin 500mg BD in T2DM at a Tertiary care hospital" Out of 100 patients, only 91 patients have completed the study. In high dose Metformin monotherapy group 7 patients did not complete the study, out of which 3 patients withdrawn due to uncontrolled blood sugar level and 4 patients lost to follow up. In Teneligliptin 20mg OD+ Metformin 500mg BD group 2 patients did not complete the study, out of which 1 patient lost to follow up and 1 patient withdrawn from the study due to uncontrolled blood sugar.
Dosage Regimen**:**

Study Group 1	Tab. Metformin 850 mg BD orally for 24 weeks (6 months).
Study Group 2	Tab. Metformin 500mg BD + Tab. Teneligliptin 20 mg daily single dose orally for 24 weeks (6 months).

After allocation into groups, patients were given tablets for 4 weeks according to the study group dosage regimen and they were asked to review for their next visit at 4th week, at 12th week and at 24th week and received tablets at each visits according to their dosage regimen. The physical, general and systemic examination was repeated at 4 th week, at 12th week and at 24th week. Fasting Blood glucose (FBS), Postprandial Blood glucose (PPBS) was done at baseline, at 4 weeks, at12 weeks, at 24weeks and Glycosylated Haemoglobin (HbA1c) was done at baseline, at 12 weeks and at 24 weeks. The drug was cont inued after the duration of study in accordance to physician's discretion.
Investigations:
Blood samples were collected with the patient fasting for at least 12 h and postprandial after 2 h. Biochemical and haematological parameters were done at central laboratory of Sree Balaji Medical College and Hospital. This was done by an automated enzymatic method. The following investigations were done during the study period:
Blood samples were collected at baseline, at 4th week, at 12th week and at 24th week.

- Fasting blood sugar level.
- Postprandial blood sugar level.

Blood samples were collected at baseline, at 12 th week and at 24th week.

- Glycosylated Haemoglobin (HbA1c)

Statistical Analysis

The study patients of Tab. Metformin 850mg BD was taken as Group 1 (M) and the Tab. Metformin 500mg BD + Tab. Teneligliptin 20mg OD was taken as Group 2 (M+T). These two groups were matched in respect to their age, sex, past history, Fasting blood sugar, postprandial blood sugar and Glycosylated Haemoglobin. Data analysis was done using Statistical Package for the Social Sciences (SPSS) version 23.0. Mean and Standard deviation (SD) was used for continuous variables. Comparison of continuous variables was done by independent students't'-test. All categorical variables were expressed as percentages. Comparison of categorical variables was analysed by Chi square test. The statistical significance was reported based on the p value, where value less than 0.05 was considered to be statistically significant.

RESULTS

The study was undertaken in the Diabetic clinic, Department of General Medicine, Sree Balaji Medical College and Hospital, Chromepet. The patient attending diabetic OPD were screened and study sample included 100 patients (as per the inclusion criteria in protocol) with T2DM who attended outpatient department. They were randomized into 2 groups such as Group– 1 (Tab. Metformin 850mg BD) and Group-2 (Tab. Teneligliptin 20mg OD + Tab. Metformin 500mg BD) and were evaluated. p value (Probability that the result is true) of <0.05 was considered as statistically significant after assuming all the rules of statistical tests. The overall results of this research study are as shown below:

Comparison of Basic Demographic Statistics

Gender and Age distribution comparison between two groups:

The demographic data was collected and evaluated. Out of 91 patients suffering from T2DM, males were predominant with 51.6% when it is compared to females 48.4%. The descriptive statistics for age is 45.93±7.37.

Table 1: Descriptive Statistics of age

	N	Minimum	Maximum	Mean	S.D
AGE	91	32	64	45.93	7.372

The gender comparison was done between Metformin (M) administered group and Teneligliptin with Metformin group (M+T). When both groups of data were compared, the males were predominant in Teneligliptin with Metformin (M+T) group (54.2%) whereas females were predominant in Metformin (M) group (51.2%). The mean age between Metformin (M) group and Teneligliptin with Metformin (M+T) group were 46±8.21 and 46±6.6, and when compared by unpaired 't' test the data was not statistically significant, as the sample selection was done randomly for the cross-sectional study.

Past History comparison between 2 groups:

The patients with past history of type 2 Diabetes mellitus was traced out in a detail between Metformin (M) administered group and Teneligliptin with Metformin group (M+T) and the data was evaluated by Chi-square test (Table 5). The Metformin (M) group with no past history of type 2 diabetes mellitus were 37.2% and Metformin with Teneligliptin (M+T) group was 31.3%, similarly the Metformin (M) group with past history of type 2 diabetes mellitus was 62.8% whereas Teneligliptin with Metformin group was 68.8%. Patient's history with the other medication was taken. The Metformin (M) group with history of other medications were 27.9% and Teneligliptin with Metformin (M+T) group was 33.3%, similarly the Metformin (M) group with no history of other medications was 72.1% whereas Teneligliptin with Metformin (M+T) group was 66.7%. When it was compared by Chi-square test, the data was not statistically significant. The glycaemic efficacy of the drug was evaluated by analysing the (mean) change in the value of HbA1C, Fasting blood sugar (FBS) and Postprandial blood sugar (PPBS).

Fasting Blood Glucose comparison between two groups:

The Fasting blood glucose (FBS) was taken from baseline with an interval of 4, 12, 24 weeks. When the data was evaluated by unpaired t test, the baseline FBS for Metformin (M) group was 132.30±19.58 whereas for Metformin with Teneligliptin (M+T) group was 150.29±17.16 and it was highly statistically significant (P<0.0005). The FBS at 4th week for Metformin (M) group (129.21±15.03) and Teneligliptin with Metformin (M+T) group (140.31±14.68) and when analysed it was highly significant at p<0.01. The FBS at 12th week for Metformin (M) group (125.12±12.45) and Teneligliptin with Metformin (M+T) group (133.48±15.53) and when analysed it was highly statistically significant p<0.006. The FBS at 24 th week for

Metformin (M) group (125.77±13.24) and Teneligliptin with Metformin (M+T) group (125.83±11.95) and when it analysed was not statistically significant (Table 2).

Therefore, Fasting blood sugar glycaemic efficacy shows more significant enhancement in Metformin with Teneligliptin (M+T) group than high dose Metformin (M) group with mean change in FBS from baseline 150.29±17.16 and 132.30±19.58 to till 24 weeks of study period 125.83±11.95 and 125.77±13.24 respectively.

Table 2 :Comparison of Fasting blood sugar (FBS) between Groups by Unpaired t-test

Groups		N	Mean	S.D	t-value	p-value
Baseline	M	43	132.30	19.58	4.670	0.0005**
	M+T	48	150.29	17.16		
4th week	M	43	129.21	15.03	3.562	0.001**
	M+T	48	140.31	14.68		
12th week	M	43	125.12	12.45	2.813	0.006**
	M+T	48	133.48	15.53		
24th week	M	43	125.77	13.21	0.025	0.980 #
	M+T	48	125.83	11.95		

No Statistical Significance at p>0.05, ** Highly Significant at p<0.01

Postprandial Blood glucose comparison between two groups:

The postprandial blood glucose was taken from baseline with an interval of 4, 12, 24 weeks. When the data was evaluated by unpaired t test, the baseline postprandial blood glucose (sugar) for Metformin(M) group was 214.63±37.99 whereas for Metformin with Teneligliptin(M+T) group was 240.02±41.7 and it was highly statistically significant (P<0.003). The postprandial blood glucose at 4th week for Metformin (M) group (199.58±32.15) and Metformin with Teneligliptin(M+T) group (216.73±38.37) and when analysed it was highly significant at p<0.024. The postprandial blood glucose at 12th week for Metformin (M) group (183.49±25.16) and Metformin with Teneligliptin (M+T) group (194.23±36.5) and when it analysed was not statistically significant. The postprandial blood glucose at 24th week for Metformin (M) group (169.77±18.03) and Metformin with Teneligliptin (M+T) group (166.65±20.08) and when it analysed was not statistically significant (Table 3). Therefore, Postprandial blood glucose glycaemic efficacy shows more significant enhancement in Metformin with Teneligliptin (M+T) group than high dose Metformin (M) group with mean changes from baseline 240.02±41.7 and 214.63±37.99 to end of 24 weeks of study period 166.65±20.08 and 169.77±18.03 respectively.

Table 3: Comparison of Postprandial blood sugar between Groups by Unpaired t-test

Groups		N	Mean	S.D	t-value	p-value
Baseline	M	43	214.63	37.99	3.024	0.003 **
	M+T	48	240.02	41.70		
4th week	M	43	199.58	32.15	2.296	0.024 *
	M+T	48	216.73	38.37		
12th week	M	43	183.49	25.16	1.616	0.110 #
	M+T	48	194.23	36.50		
24th week	M	43	169.77	18.03	0.777	0.439 #
	M+T	48	166.65	20.08		

#No Statistical Significance at p>0.05
* Statistical Significance at p<0.05
** Highly Significant at p<0.01

Glycosylated haemoglobin (HbA1c) comparison between both the groups:

The glycosylated haemoglobin A1C (HbA1c) was taken from baseline with an interval of 12, 24 weeks. When the data was evaluated by unpaired t test, the baseline glycosylated haemoglobin A1C level for Metformin (M) group was 7.63±0.50 whereas for Metformin with Teneligliptin (M+T) group was 7.83±0.51 and it was not statistically significant. The glycosylated haemoglobin A1C level at 12th week for Metformin (M) group (7.47±0.51) and Metformin with Teneligliptin (M+T) group (7.54±0.47) and when it analysed was not significant. The glycosylated haemoglobin A1C level at 24th week for Metformin (M) group (7.27±0.45) and Metformin with Teneligliptin (M+T) group (7.1±0.42) and when it analysed was not statistically significant (Table 4). Therefore, HbA1c efficacy shows more consistent significant

enhancement (improvement) in Metformin with Teneligliptin (M+T) group than high dose Metformin (M) group with mean change of glycosylated haemoglobin A1C from baseline 7.83±0.51 and 7.63±0.50 to end of study period 7.1±0.42 and 7.27±0.45 respectively.

Table 4: Comparison of Haemoglobin A1C between Groups by Unpaired t-test

Groups		N	Mean	S.D	t-value	p-value
Baseline	M	43	7.63	0.50	1.962	0.053 #
	M+T	48	7.83	0.51		
12th week	M	43	7.47	0.51	0.637	0.526 #
	M+T	48	7.54	0.47		
24th week	M	43	7.27	0.45	1.845	0.068 #
	M+T	48	7.10	0.42		
# No Statistical Significance at p>0.05 level						

Adverse effects comparison between both the groups:

Adverse effects between both the groups were compared at each visit 4 weeks, 12 weeks and 24 weeks. At the end of study period Metformin (M) group has 12(13%) patients with gastrointestinal disturbances and Metformin +Teneligliptin (M+T) has 9(9%) patients with gastrointestinal disturbances (7 patients) and nasopharyngitis (2 patients). Table5.

Table 5: Adverse effects comparison between both the groups

GROUPS	GASTROINTESTINAL DISTURBANCES	NASOPHARYNGITIS	OTHERS
METFORMIN(M)	12	0	0
METFORMIN+ TENELIGLIPTIN (M+T)	7	2	0

DISCUSSION

This study was aimed "To compare the effectiveness and safety of Metformin 850mg BD versus Teneligliptin 20mg OD as add on to Metformin 500mg BD in type 2 diabetes mellitus at a tertiary care hospital". The research was started with 100 patients suffering from type 2 DM. They were divided randomly into Group 1 taking Tab. Metformin 850mg BD daily and Group 2 taking Tab. Metformin 500mg BD + Tab. Teneligliptin 20mg OD daily. Among 100 patients, only 91 were completed the research study. The prevalence of T2DM was greater in males than in females. The males were higher in Metformin + Teneligliptin group (54.2%) whereas females were higher in Metformin group (51.2%). As per the previous research carried out by Bennett et al 62and Howteerakul et al.,63 the incidence of Type 2 Diabetes Mellitus among men was higher than women which is consistent with our study. Type 2 DM is commonly seen in middle-aged persons, especially after 50 years of age. 61 The mean age in this (research) study was in the range of 40 –50 years, this fact is supported by the study conducted by Kishimoto et al. 43 The mean age between Metformin (Group 1) and Teneligliptin + Metformin (Group 2) were 46±8.21 and 46±6.6 respectively fig; 7.This study showed a past history of T2DM in 65.9 % of patients (fig; 8). Type 2 DM has significant relation with family history; if any one or both parents had Type 2 DM it can be transferred from one generation to another at one point in their life. This was also similar with Bennett et al. wider prospective study [6]. In this research, the average Diabetes Mellitus period was 0 –10 years, which is similar with the preceding study by Jeon et al.[7]. The glycemic efficacy was evaluated by analyzing the mean change in the value of Fasting Blood glucose levels (FBS), postprandial blood glucose levels (PPBS) and glycated hemoglobin (HbA1c). The patients showed an enhancement in their glycemic parameters such as Fasting Blood glucose levels (FBS), postprandial blood glucose levels (PPBS) and glycated hemoglobin (HbA1c) in both the groups throughout the study period. At the end of study period (24 weeks), high dose Metformin group has showed the following results, mean change of FBS, PPBS and HbA1c were reduced from 132.30±19.58mg/dl, 214.63±37.99mg/dl and 7.63±0.50 to 125.83±11.95mg/dl, 169.77±18.03 and 7.27±0.45 respectively whereas in Metformin and Teneligliptin combination therapy, the results were mean change of Fasting Blood glucose levels (FBS), postprandial blood glucose levels (PPBS) and glycated haemoglobin (HbA1c) were significantly decreased from 150.29±17.16mg/dl, 240±41.70mg/dl and 7.83±0.51%, to 125.83±11.95mg/dl,166.65±20.08 mg/dl and 7.10±0.42%,

respectively (Table 2,3,4). The results are perfectly showing consistent significant improvement of HbA1C with the Teneligliptin + Metformin group when compared to a Metformin group from starting (baseline) to the end of (24 weeks) study period. Although high dose Metformin monotherapy shows decrease in HbA1C, it is lesser than the Metformin + Teneligliptin group as depicted in previous studies. As per the previous study done by Kim et al. [8] shows that Teneligliptin addition to Metformin therapy shows a significant decrease in glycaemic parameters such as FBS, PPBS and HbA1C values in type 2 DM Korean patients whose glycaemic status was not managed with metformin alone. In another study conducted by Sujoy et al. [9] (TREAT-INDIA), there was statistically significant enhancement in mean glycated haemoglobin (HbA1c), Fasting Blood glucose (FBS) and Postprandial Blood sugar (PPBS) with Teneligliptin monotherapy. Mean changes in mean glycated haemoglobin (HbA1c), Fasting Blood glucose (FBS) and Postprandial Blood sugar (PPBS) were 1.37±1.15%, 51.29±35.41 mg/dl, and 80.89±54.27 mg/dl, respectively. Recently Batta Raghuveer et al., [10] was done another study to access the effectiveness of Teneligliptin with metformin in T2DM patients. The effectiveness was evaluated by measuring the mean change in the FPG, PPBG, and glycated haemoglobin (HbA1c) levels at the end of 24 weeks. The combination therapy of Metformin with Teneligliptin was shown a clinically significant improvement in HbA1C values. This study described that Teneligliptin is an effective add on drug in uncontrolled type 2 DM patients with metformin monotherapy. Metformin with Teneligliptin was effective and well tolerable in type 2 diabetes mellitus patients and has a long half -life of 26.9 h with a special pharmacokinetic benefit that makes easy once-daily administration irrespective of diet. It has dual mode of elimination through renal route and hepatic route; hence, it can be safely administered in renal dysfunction patients. No dose modification is needed for mild to moderate hepatic dysfunction. Appropriate approach to diabetes control would include not only glycaemic parameters but also early protection of the function of islet cells of pancreas and avoiding the progress of the disease [11]. Teneligliptin was thoroughly studied in various populations (patient profiles) of T2DM as monotherapy or with other anti-diabetic agents as combination therapy. These studies comprised both short and long term studies from 12 to 52 weeks and have stated a significant decrease in blood sugar level with an improvement in HbA1c of 0.8% –0.9% reduction in 3 months (12 weeks), which was sustained upto 52 weeks of Teneligliptin therapy. These studies has also proved that it can be used as monotherapy and also as dual therapy. Additionally, there are pleiotropic effects of Teneligliptin in terms of enhancement in vascular endothelial function, lipid profile levels and body weight. Teneligliptn reported favourable tolerability with few Adverse Effects [12]. Dose adjustment is not required in renal dysfunction or End Stage Renal Disease and in hepatic dysfunction patients. Though as of now Teneligliptin did not point any serious adverse effect, studies more than 52 weeks are still required for the long term effectiveness and safety of Teneligliptin therapy. Adverse effects were compared and analysed, about 13% and 10% were reported in Metformin and Teneligliptin + Metformin group respectively [Table 5]. No serious adverse effects were reported in both the groups [13]. In our study, both the study drugs shows improvement in their glycaemic profile and also it has additional pleiotropic effects. Therefore,DPP-4 inhibitor Teneligliptin 20mg OD with Metformin 500mg BD shows significant improvement when compared to high dose Metformin 850mg BD monotherapy in type 2 DM patients which is in consistence with previous studies.

CONCLUSION

This study outcome revealed that Teneligliptin 20mg OD plus Metformin 500mg BD is safer and efficacious compared to Metformin 850mg BD in Type 2 Diabetes Mellitus patients. Both treatment group provided enhancement in mean HbA1c values. But the decline of mean HbA1c was very much superior in Teneligliptin with Metformin group compared to Metformin group. Teneligliptin 20mg OD plus Metformin 500mg BD group is also efficacious in significant decrease in Fasting blood sugar (FBS), Postprandial blood sugar (PPBS) when compared to metformin 850mg BD daily. The prevalence and severity of adverse effect is less in Teneligliptin 20mg OD plus Metformin 500mg BD group when compared with metformin 850mg BD group. To conclude DPP-4 inhibitor Teneligliptin 20mg OD serves as an appropriate add-on to Metformin 500mg BD to enhance the glycaemic control and to delay exhaustion of pancreatic islet cell function and may be an effective and safe treatment option in type 2 Diabetes Mellitus with good patient tolerability.

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