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Original Article

Pharmacology Section

Effect of Teneligliptin versus Glimepiride on Tumour Necrosis Factor Alpha and High Sensitivity C-Reactive Protein in Type 2 Diabetes Mellitus Patients Treated with Metformin: A Randomised Double-blind Parallel Group Study

MALEHA BUTUL[1], PINGALI USHARANI[2], MVS SUBBALAXMI[3]

ABSTRACT

Introduction: Inflammatory markers like Tumour Necrosis Factor-α (TNF-α), C-Reactive Protein (CRP), and Interleukin-6 (IL-6) play intermediary role in insulin resistance, pathogenesis of Type 2 Diabetes Mellitus (T2DM) and its complications. Hence, antidiabetic drugs having anti-inflammatory effects may play an important role in management of T2DM and prevention of its complications.

Aim: To study the effect of glimepiride versus teneligliptin on TNF-α, high sensitivity C-reactive Protein (hsCRP) and Diabetic Peripheral Neuropathy (DPN) in T2DM patients on metformin.

Materials and Methods: The randomised, double-blind, parallel group study was conducted in Nizam's Institute of Medical Sciences, Hyderabad, Telangana, India, from April 2018 to October 2019. Total 44 participants were screened and 40 participants of either gender, age range of 35-65 years, Body Mass Index (BMI) ≥25-≤35 kg/m^2 and Fasting Blood Sugar ≥126 to ≤200 mg/dL, and glycosylated-haemoglobin (HbA1c) 7.0 to ≤10.0% were included into the study. The T2DM patients (N=40) on metformin (1500-2500 mg/day) were randomised to receive glimepiride (2 mg/day) and teneligliptin (20 mg/day) in group A and group B for 12 weeks, respectively. TNF-α, hsCRP and Vibration-Perception Threshold (VPT) at baseline, 4 weeks and 12 weeks were evaluated for all participants. FBS, HbA1c, Adverse Drug Reactions (ADRs) were also recorded. Unpaired t-test and repeated-measures Analysis of Variance (ANOVA) for normally-distributed variables using Shapiro-Wilk's test was done. Mann-Whitney and Friedman's test for non normally distributed variables; for between-group and within-group analysis, respectively were done.

Results: Forty T2DM patients (17 males and 23 females) with mean age of 49.45±6.8 and 50.3±7.9 years, were studied. The mean TNF-α level reduced significantly, in group B (159.25±58.58 to 83.15±26.18 pg/mL; p-value<0.001) from baseline to 12 weeks. Similar significant reduction was seen in the group A (175.2±66.13 to 116.15±63.32 pg/mL; p-value<0.05). There was significant reduction observed in mean VPT-scores (25±6 to 18.0±5.22 V; p-value <0.001) and (26±12.11 to 25±12 V; p-value <0.05) in group B and group A, at 12 weeks, respectively. However, both study groups showed non significant decrease in mean hsCRP levels at 12 weeks. There was a non significant reduction in all study parameters at four weeks. Mean percentage reduction of 34% and 44% in TNF-α, 13% and 11% in hsCRP and 7% and 27% in VPT-scores was observed in group A and group B, respectively at 12 weeks. Improvement in FBS and HbA1c levels (p-value <0.001) was observed in both study groups. Both treatments were tolerated well and no serious adverse drug reactions were observed.

Conclusion: Teneligliptin by reducing TNF-α level, demonstrated modest anti-inflammatory activity along with metformin, by 12 weeks. It also improved VPT-scores. Glimepiride showed lesser degree of anti-inflammatory activity compared to teneligliptin. Both study drugs did not affect hsCRP levels.

Keywords: Antidiabetic drugs, Diabetic peripheral neuropathy, Inflammatory markers, Vibration-perception threshold

INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) is characterised by hyperglycaemia due to insulin-deficiency and peripheral insulin resistance. It is estimated that, 77 million Indian individuals had diabetes in 2019, and this figure is expected to rise to over 134 million by 2045 in India [1].

Inflammatory marker like Tumour Necrosis Factor-α (TNF-α), C-Reactive Protein (CRP), and Interleukin-6 (IL-6) play intermediary-role in insulin resistance, pathogenesis of T2DM and its complications [2]. TNF-α biomarker influence intermediary metabolism and act as a link between inflammation and insulin resistance. Due to underlying inflammation, there is increased release of cytokines like TNF-α in skeletal muscles as well as liberation of CRP from the liver resulting in insulin resistance in T2DM [3]. The TNF-α bind to TNF receptor-1 thus, activating sphingomyelinase and cascade of events resulting in decrease in Glucose Transporter-4 (GLUT-4) translocation and glucose uptake [4]. Role of TNF-α in reducing insulin production from β-cell, was also reported [5].

The CRP is an independent risk determinant for newly diagnosed T2DM [6]. Clinically, high sensitivity C-Reactive Protein (hsCRP) is more stable and integrated measure of low-grade inflammation. Chronic low-grade underlying inflammation due to elevated CRP might be a cause for aetiology and manifestation of T2DM. A prospective study reported significantly higher baseline CRP levels in people, who later developed T2DM and its complications providing link between inflammation and development of micro and macrovascular-complications, respectively [7]. In addition, subjects with high CRP levels had 2.2 and 8.1 times elevated-risk

of pre-diabetes and T2DM, respectively even after adjusting for confounders like age, gender, and Body Mass Index (BMI) [8]. It has been reported that, elevated CRP concentrations increase with increasing HbA1c levels [9]. During disease progression, both TNF-α and CRP level increase in uncontrolled diabetes. Raised serum TNF-α level in T2DM patients were found to be associated with increased BMI, fasting insulin levels and insulin resistance [10]. TNF-α has also shown strong and positive correlation with duration of disease. Increased levels of TNF-α (13.5 pg/mL) levels after adjusting for confounders, were also associated with severity of diabetic complication [11].

The underlying enhanced inflammatory responses due to increase in TNF-α and CRP production during diabetes progression may be responsible for Diabetic Peripheral Neuropathy (DPN). Vibration Perception Threshold (VPT) test, a gold standard, cost-effective bedside screening procedure helps in diagnosis of DPN [12]. Hence, pharmacological strategies utilising anti-inflammatory effects of anti-diabetic drugs in treatment of T2DM is important to achieve a comparable quality of life near to those of healthy people. Near normal HbA1c significantly decreases risk of macro and microvascular complications.

The beneficial anti-inflammatory effects of metformin, pioglitazone in T2DM are also well-established [13]. Sulfonylureas (SUs) showed anti-inflammatory properties by blocking potassium ion (K+) channels and suppressing TNF-α production from activated macrophages [14]. Glibenclamide and gliclazide demonstrated improvement in DPN in diabetic animals by inhibiting the TNF-α production [15]. Anti-inflammatory activity of Dipeptidyl Peptidase-4 Inhibitor (DPP-4I) in T2DM patients and improvement in DPN in animals was also reported [13,16,17].

Teneligliptin, is a DPP-4I approved for commercial use in India in 2015 for treatment of T2DM [18]. It has similar antidiabetic efficacy and safety profile compared to other drugs of its class [19]. But currently, limited information on effect of teneligliptin and glimepiride on inflammatory cytokines and their role in DPN is available in T2DM patients. Even though these inflammatory markers are thought to be well understood, they have limited acceptance as clinical markers in regulation of T2DM. It could be due to variation in their levels among various ethnic groups [20-22]. Therefore, studies are required to show their anti-inflammatory action in T2DM. And if, these drugs demonstrate anti-inflammatory effects, these may reduce the burden on healthcare cost in Indian population.

Hence, the present study was undertaken to study effect of teneligliptin versus glimepiride in T2DM patients on metformin. Primary-endpoints were change in serum concentrations of TNF-α and hsCRP at 12 weeks and secondary endpoints were change in VPT scores, FBS, HbA1c and incidence of adverse effects at 12 weeks.

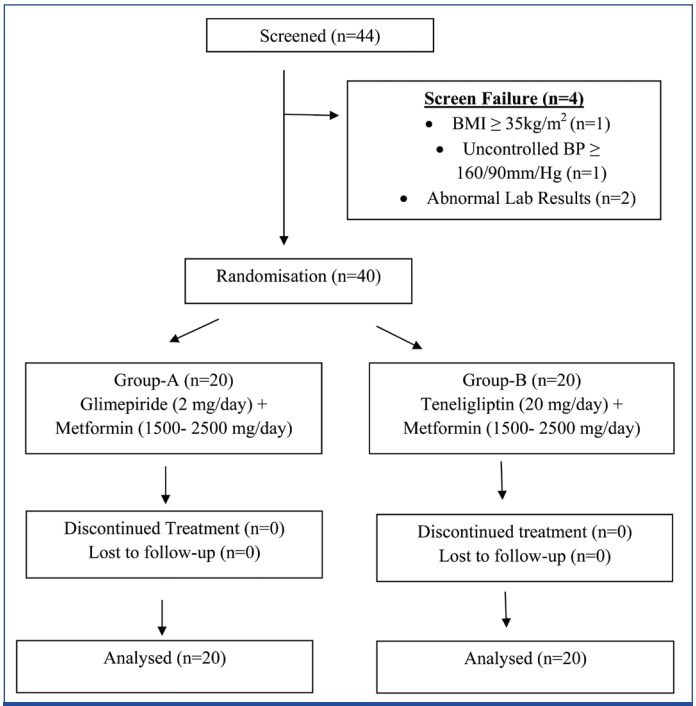
MATERIALS AND METHODS

A randomised, double-blind, parallel group study was conducted from April 2018 to October 2019 at Nizam's Institute of Medical Sciences, Hyderabad, Telangana, India (tertiary care hospital). The Institutional Ethics Committee (IEC) had approved the study (ESGS No. 672/2018, dated 06-03-2018). Written informed consent was taken from all the subjects prior to participation in the study. The study is registered with the Clinical Trials Registry-India (CTRI number= CTRI/2018/03/012603). Uncomplicated T2DM patients (n=44), for past 1-3 years and on stable oral dose of metformin 1500-2500 mg/day and naïve to glimepiride and teneligliptin before enrollment were recruited for screening. They were on a stable dose of antihypertensives for maintenance of blood pressure ≤160/90 mmHg.

Inclusion criteria: Participants of either gender and age between 35-65 years, BMI ≥25 kg/m^2 to ≤35 kg/m^2 and fasting blood sugar ≥126 mg/dL to ≤200 mg/dL, and glycosylated-haemoglobin (HbA1c) 7 to≤10% were included in the study.

Exclusion criteria: Participants with blood pressure >160/90 mmHg, HbA1c>10%, hsCRP >3 mg/L, impaired renal, liver-function test ≥3ULN, abnormal lipid-profile, pregnancy, lactation, other concomitant-medications, hypersensitivity to drugs and participation in other clinical trials in past three months were excluded from the study.

Sample size calculation: To detect 20±20 pg/mL fall in TNF-α level [16] about 32 participants were found sufficient at α-value=0.05 and 80% power. Considering screen-failure (15%) and dropout rate (15%), 44 participants were screened to enroll 40 participants in the study [Table/Fig-1].



[Table/Fig-1]: Consolidated Standards of Reporting Trials (CONSORT) Participant Flow Diagram.

Randomisation was done according to a computer-generated randomisation-sequence, using 10' random permuted-blocks of four patients each, to enroll 40 participants in the study.

Group A: Glimepiride (2 mg/day) (AMARYL, Sanofi-India, Ltd.) with metformin (1500-2500 mg/day) for 12 weeks.

Group B: Teneligliptin (20 mg/day) (ZITEN, Glenmark-Pharmaceuticals) with metformin (1500-2500 mg/day) for 12 weeks.

Study Procedure

Both investigator and participants were blinded; dispense of study medications were performed by a third-person not related to study. Tablets were provided in identical sequentially-numbered containers. The study medications were dispensed to participants at each visit according to their randomisation. They were instructed to take medicine at the same time of the day. Unblinding of randomisation was done 24 hours after last visit of the participant.

Evaluation of TNF-α, hs-CRP levels and VPT scores were done at baseline, 4 weeks and 12 weeks. FBS was recorded at baseline, 4 weeks, 8 weeks and 12 weeks. HbA1c was done at baseline and 12 weeks. Physical examination, vitals, safety and tolerability assessments were done at every review visit. Concomitant medications taken and Adverse Drug Reactions (ADRs) reported were recorded in Case Record Forms (CRF). Medication compliance was monitored by pill-count method. At the end of treatment, participants were asked to report to the clinician for their standard clinical care.

Evaluation Methods

TNF-α: Detection-limit-7.8-500 pg/mL (human serum) evaluated by Boster's human TNF-alpha symbol, Enzyme Linked Immunosorbent Assay (ELISA) Kit (Boster-Biological-Technology Co).

hsCRP: Levels estimated by immunoturbidimetry method (Beckman-Coulter AU640) (Assay range: 0.2–155.86 mg/L).

VPT: It was measured by Vibrometer-VPT® (Diabetic foot care, Madras Engineering Service, India) by single observer. A probe was kept at great-toe, base of 1st, 3rd and 5th metatarsal, in-step, and heel in right and left feet. Voltage was increased from 0 to 50 V and mean-VPT recorded. Grading of VPT score 15 V (normal), 16-25 V (Grade-I) and >25 V (Grade-II) as per manufacturer manual was followed.

FBS: It was measured by glucose-hexokinase method on Siemens-RXI-analyser

HbA1c: It was estimated using HPLC on Bio-Rad-D10.

STATISTICAL ANALYSIS

Data was presented as Mean±Standard Deviation (SD). Unpaired t-test and repeated-measure Analysis of Variance (ANOVA) for normally-distributed variables using Shapiro-Wilk's test was done. Mann-Whitney and Friedman's test for non normally distributed variables; for between-group and within-group analysis respectively were done. A p≤0.05 was considered statistically significant. Incidence of adverse effects was presented as proportions. Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS, Armonk, NY:IBM-Corp) version 20.0.

RESULTS

Total 40 T2DM patients (17 males and 23 females) with mean age 49.88±7.26 years and BMI 27.81±2.43 kg/m^2 were randomised to receive the study medications. Demographic and clinical characteristics for both study groups are shown in [Table/Fig-2]. Both study groups were homogenous at baseline (p-value >0.05).

Variables	Group A (n=20) (Mean±SD)	Group B (n=20) (Mean±SD)	p-value
Age (years)	49.45±6.8	50.3±7.9	0.606
Gender (Male/Female)	10/10	7/13	0.337
Weight (Kg)	65.42±6.88	69.5±8.87	0.536
Body mass index (kg/m^2)	28.3±2.7	27.3±2.2	0.250
Fasting boold sugar (mg/dL)	161.5±18.8	158.45±20.8	0.507
HbA1c (%)	7.44 (7.1-8.3)†	7.73 (7.7-8.6)†	0.606
Triglycerides (mg/dL)	117.8±14.9	117.15±16.21	0.896
Total cholesterol (mg/dL)	135.5±18.8	136.3±23.1	0.911
LDL cholesterol (mg/dL)	100.4±20.4	97.6±21.4	0.715
HDL cholesterol (mg/dL)	39.15±1.81	40.55±3	0.108
No. of patients on metformin (1500-2000 mg/day)	17	14	-
No. of patients on metformin (2500 mg/day)	3	6	-
No. of patients on stable dose of antihypertensives (n)	15/20	12/20	-

[Table/Fig-2]: Demographic data of study participants.
Data presented as mean±SD (Standard Deviation) †-median and Range

1. Tumour Necrosis Factor-α level (TNF-α) pg/mL:

Within group analysis: There was a significant reduction in mean TNF-α level in group A and group B from baseline to 12 weeks. Both groups showed non significant reduction from baseline to four weeks. However, the mean TNF-α level reduced significantly from 4 to 12 weeks in group B, but not in group A [Table/Fig-3].

Between group analysis: There was significant reduction observed in mean TNF-α level, when group A vs group B comparisons were done at 12 weeks using unpaired t test. But non significant change was observed at four weeks and at baseline [Table/Fig-3]. Mean absolute change (-59.05±52.13 pg/mL) vs (-76.1±54.19 pg/mL) in TNF-α levels in group A vs group B, respectively, was observed at 12 weeks.

Groups	Levels in T2DM patients at 0 week (Mean±SD)	4 week (Mean±SD)	12 week (Mean±SD)	p-value
TNF-α (pg/mL)				
Group A	175.2±66.13	141.85±72.5	116.15±63.32	0 to 4 weeks p-value=0.266
				0 to 12 weeks p-value <0.001
				4 to 12 weeks p-value=0.129
Group B	159.25±58.58	140.15± 73.12	83.15± 26.18	0-4 weeks p-value=0.095
				0-12 weeks p-value <0.001
				4-12 weeks p-value=0.002
p-value	0.424	0.942	0.038	
High sensitivity C-reactive protein (mg/L)				
Group A	2.71±0.79	2.55±0.73	2.29±0.64	0 to 4 weeks p-value=0.083
				0 to 12 weeks p-value=0.011
				4-12 weeks p-value=0.084
Group B	2.78±0.94	2.54±0.95	2.40±0.76	0 to 4 weeks p-value=0.100
				0 to 12 weeks p-value=0.02
				4-12 weeks p-value=0.544
p-value	0.144	0.971	0.626	
Vibration-perception threshold (V)				
Group A	26±12.11	25±12.28	25±12	0 to 4 weeks p-value=0.05
				0 to 12 weeks p-value <0.001
				4-12 weeks p-value=0.071
Group B	25±6	22±6.08	18±5.22	0 to 4 weeks p-value=0.001
				0 to 12 weeks p-value <0.001
				4-12 weeks p-value=0.001
p-value	0.597	0.350	0.028	

[Table/Fig-3]: Effect of glimepiride and teneligliptin on TNF-α (pg/mL), hsCRP (mg/L) and VPT (V) levels in T2DM patients.
Within group analysis was done using repeated-measure ANOVA and between group analyses was done using unpaired t-test. p<0.05 considered significant. TNF-α: Tumour necrosis factor-α; hsCRP: High sensitivity C-reactive protein; VPT: Vibration-perception threshold

2. High sensitivity C-Reactive Protein levels (mg/L):

Within group analysis: There was a significant reduction observed in mean hsCRP level in group A and group B from baseline to 12 weeks. Further analysis showed non significant reduction in mean hsCRP level from baseline to four weeks and from four week to 12 weeks in both study groups [Table/Fig-3].

Between group analysis: Non significant reduction in mean hsCRP level in group A vs group B was observed at 4 and 12 weeks. Both groups were homogenous and comparable at baseline [Table/Fig-3]. Mean absolute change in hsCRP level was observed at 12 weeks, respectively (-0.42±0.61 mg/L vs -0.37±0.49 mg/L).

3. Vibration-perception threshold (V):

Within group analysis: VPT scores improved significantly in both groups from baseline to four weeks and 12 weeks. Significant

improvement in the VPT scores were noticed from week four weeks to 12 week in group B, but not in group A [Table/Fig-3].

Between group analysis: There was significant improvement in VPT scores in both study groups at 12 weeks. Similar change was not observed at four weeks. Both groups were comparable at baseline [Table/Fig-3].

Mean absolute change of in VPT scores was observed in group A vs group B, respectively at 12 weeks (-1.7±1.13 V and -6.8±2.8 V).

Differences in percentage reduction in TNF-α, hsCRP levels and VPT scores were observed between the groups [Table/Fig-4].

Groups	Percentage change (%) at 12 weeks		
	TNF-α	hsCRP	VPT
Group A	-34	-13	-7
Group B	-44	-11	-27

[Table/Fig-4]: Percentage change (%) in TNF-α, hsCRP level and VPT scores with glimepiride and teneligliptin in T2DM patients.

4. Glycaemic control, body weight and BMI

Within group analysis: There was a significant reduction in mean FBS levels from baseline to 4, 8 and 12 weeks and median HbA1c levels from baseline to 12 weeks in both groups (p-value <0.001) [Table/Fig-5,6]. There were non significant changes in body weight and BMI from baseline to four weeks, eight weeks and 12 weeks in group A and group B (p-value <0.001).

Groups	Fasting blood sugar (mg/dL)				
	0 week (Mean±SD)	4 week (Mean±SD)	8 week (Mean±SD)	12 week (Mean±SD)	p-value
Group A	160.6±15.6	152±14.5	143.45± 12.2	132.7± 10.3	0-4 - <0.001 0-12 - <0.001 4-12 - <0.001 8-12 - <0.001
Group B	155.9±17.08	147.35± 15.15	141.7± 14.1	130.6± 13.68	0-4 - <0.001 0-12 - <0.001 4-12 - <0.001 8-12- <0.001
p-value	>0.05	>0.05	>0.05	>0.05	

[Table/Fig-5]: Effect of glimepiride and teneligliptin on FBS (mg/dL) levels at 12 weeks. Within group analysis was done using repeated-measure ANOVA and between group analyses was done using unpaired t-test. p<0.05 was considered significant

Groups	HbA1c (%)		
	0 week (Median and Range)	12 week (Median and Range)	p-value
Group A	7.61 (7.2-8.3)	6.94 (6.4-7.5)	<0.001
Group B	7.73 (7.1-8.6)	7.18 (6.4-7.9)	<0.001
p-value	>0.05	>0.05	

[Table/Fig-6]: Effect of glimepiride and teneligliptin on HbA1c (%) levels at 12 weeks. Within group analysis was done using Wilcoxon Rank test and between group analyses was done using Mann Whitney test. p<0.05 considered significant

Between group analysis: Non significant difference in mean FBS levels at four weeks, eight weeks and 12 weeks and median HbA1c levels at 12 weeks was noticed in both study groups [Table/Fig-5,6].

Safety analysis: There were no serious untoward events or adverse drug reactions observed during the study. Nausea (n=2) in group A and constipation (n=3) and abdominal pain (n=1) in group B were self-limited. Medication compliance (>90%) in all participants was verified by pill-count method. All subjects tolerated the therapy well. None of the participants reported hypoglycaemia or discontinued the study or withdrew from the study.

DISCUSSION

Diabetes being a progressive disease, most of the uncontrolled T2DM patients, may require antidiabetic drugs having additional anti-inflammatory effects. These drugs can be combined as add-on drugs to metformin in order to control symptoms and complications of T2DM. Hence, in the present study, an effort was made to evaluate the anti-inflammatory role of teneligliptin 20 mg/day in comparison to glimepiride 2 mg/day in T2DM patients not adequately controlled by metformin therapy. Teneligliptin may be added to metformin as it has similar beneficial properties as other gliptins i.e. reduction in HbA1c (0.8%-0.9%) low incidence of hypoglycaemia and benefits of weight neutral effects, less seen with glimepiride [23].

Teneligliptin is reported to be a potent DPP-4I with enhanced potency and selectivity; and having fivefold higher activity than sitagliptin [24]. It inactivates DPP4 activity at a lower IC50 (0.34 nmol/L) than other DPP-4I [24]. Rise in new β-cells, inhibition of β-cell apoptosis, effectiveness in obesity, metabolic syndrome and improvement in vascular endothelial function are few additional effects of teneligliptin [23]. Therefore, looking at the beneficial effects of teneligliptin, it could be understood that addition of teneligliptin to metformin at the earliest may result in better control of both glycaemic and inflammatory status in T2DM as compared to glimepiride.

The present study evaluated the effects of teneligliptin versus glimepiride on TNF-α and hsCRP levels in T2DM patients treated with metformin. Effect on DPN was also assessed by analysing VPT-scores. The results of the study, demonstrated significant decrease in TNF-α level and an improving trend in VPT scores in group B compared to group A at 12 weeks. However, similar change was not observed in hsCRP levels in both study groups. All participants showed improvement in FBS and HbA1c at 12 weeks which was almost similar in both study groups. Treatment goal of 130 mg/dL FBS and ≤7.5% HbA1c was achieved, which is in accordance with standards of medical care and thus, up-titration was not required for glimepiride and teneligliptin doses in treatment groups during the study duration. There was no significant change observed in body weight and BMI during study period.

Effect of teneligliptin on TNF-α and hsCRP level: A study by Vinendra MP and Sunita SG, showed statistically significant (p-value <0.05) reduction in TNF-α in teneligliptin 20 mg/day treated group (15.348±1.69 to 14.597±1.65 pg/mL) from baseline to 24 weeks respectively [25].

The present study results, support the previous clinical study where in teneligliptin demonstrated modest but statistically significant anti-inflammatory effects, better than glimepirideat 12 weeks. Appreciable effect on hsCRP level could not be demonstrated by both drugs probably due to short duration of study. Even though TNF-α is the hall mark of inflammation in T2DM, reduction in CRP would also be requiredfor a meaningful reduction in inflammation. As CRP is an established biomarker for coronary risk associated with diabetes, it would have been of great importance, if present study could have demonstrated reduction in hsCRP levels. Longer study duration may probably be required to highlight reduction in hsCRP levels.

Effect of glimepiride on TNF-α and hsCRP level: Sulfonylureas (SUs) produce anti-inflammatory effects either by preventing the inflammatory responses by MAPKs/NF-κb-dependent pathway or suppressing production of cytokines like TNF-α and CRP [26]. Study by Koshiba K et al., reported significant reduction in TNF-α and hsCRP levels in T2DM patients in glimepiride group compared to glibenclamide and insulin groups [27]. A decrease in TNF-α (2.67 to 1.45 pg/mL) and hsCRP (0.048 to 0.022 mg/L) level in T2DM patients at 28 weeks was reported. There was 45% reduction in TNF-α level at 28 weeks. Simó R et al., reported an absolute decrease in hsCRP level (-0.2 mg/L) at 36 months in glimepiride group. Glimepiride with rosiglitazone, empagliflozin and exenatide added to metformin, reduced hsCRP serum concentrations [28].

The present study results showed a decrease in TNF-α, but not in hsCRP level with glimepiride administration and moreover, decrease in TNF-α level with glimepiride was less compared to teneligliptin

treatment. In addition, TNF-α and hsCRP levels did not decrease at four weeks in both study groups. It could be possible that, patients at onset of study were only on treatment with metformin and naïve to glimepiride and teneligliptin. Antidiabetic agents may perhaps require adequate time of 2-4 weeks to decrease inflammatory markers and to affect IRS-1 and translocation of GLUT4 in order to improve insulin resistance.

Effect of Teneligliptin and Glimepiride on VPT: Because of insidious nature of diabetes, chronic diabetic complications are often unavoidable in T2DM patients. In addition to hyperglycaemia and dyslipidaemia, underlying inflammatory markers could be responsible for development and progression of DPN [29]. TNF-α regulated CRP, might result in neuronal ischaemia or necrosis resulting in nerve conduction block leading to nerve damaging symptoms and diabetic foot ulcers [29].

Administration of TNF-α to diabetic rats, decreased Motor Nerve Conduction Velocity (MNCV) of sciatic nerve compared to non diabetic rats [17]. Inhibitory effects of certain drugs on TNF-α production and as a result amelioration of experimental diabetes neuropathy was reported. Studies reported suppression of TNF-α and CRP production in diabetes animals by sitagliptin or glipizide reduced the severity of DPN, either by increase in myelinated fiber density in diabetic rats or improvement in nerve conduction velocity [17].

In the present study, presence of grade II mean VPT scores, uncontrolled hyperglycaemia (HbA1c ≥7.5%) and higher TNF-α and hsCRP levels at baseline were observed in both study groups when treated with metformin alone. Add-on intervention with teneligliptin showed significant improving trend in VPT scores, when, between and within group comparisons were done at 12 weeks. Negligible improvement was also observed in glimepiride group at 12 weeks. Improvement in VPT scores from grade II to grade I, by teneligliptin was achieved within 12 weeks. Reduction in TNF-α level by teneligliptin treatment, perhaps contributed to this improvement. Teneligliptin may, thus, help in correction of both hyperglycaemia and underlying inflammation of neurons. It may also improve diabetic neuropathy by inhibiting infiltration of macrophages responsible for nerve damage.

Prolonged administration of teneligliptin along with metformin may probably delay development of diabetic foot ulcers resulting due to underlying inflammatory pathology. Hence, anti-diabetic drugs that reduce inflammation and prevent diabetes complications, in addition to improving glycaemic status are required for better outcomes in T2DM.

Anti-inflammatory effect of anti-diabetic agents resulting in improvement in DPN symptoms has not been thoroughly investigated in Indian population. The present study is first of its kind, to evaluate action of teneligliptin verses glimepiride on inflammatory markers and on clinical improvement in in symptoms of DPN. Appropriate anti-inflammatory serum markers like TNF-α and hsCRP were used to observe their involvement in T2DM and complications. Both inflammatory markers selected were sensitive and robust [30]. They provide closer associations and better prediction of risk outcomes, than other markers of inflammation.

Limitation(s)

The short duration of study is a major limitation. Other nerve function test like touch and temperature perception could have also been evaluated. In addition, adverse drug reactions on long-term use of glimepiride with metformin and teneligliptin with metformin could not be assessed.

CONCLUSION(S)

Teneligliptin may thus help in correction of both hyperglycaemia and underlying inflammation of neurons. It may also improve diabetes neuropathy by inhibiting infiltration of macrophages responsible for nerve damage. Moreover, it may be an effective substitute for 1st and 2nd generation gliptins and sulfonylureas, when added to metformin at earliest; without waiting for maximum dose of metformin to be achieved. Hence, teneligliptin by virtue of its anti-inflammatory and hypoglycaemic effects and availability at affordable price range in India, may be chosen as an add on drug for effective management of hyperglycaemia and associated neurological complications. It may improve symptoms of diabetic neuropathy. However, long term studies with a larger sample-size along with objective assessment of DPN could help in strengthening this objective further; as amelioration of DPN may require longer duration to translate into clinical improvement.

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PARTICULARS OF CONTRIBUTORS:
1. Assistant Professor, Department of Pharmacology, Shadan Institute of Medical Sciences, Hyderabad, Telangana, India.
2. Professor and Head and Guide, Department of Clinical Pharmacology and Therapeutics, Nizam's Institute of Medical Sciences, Hyderabad, Telangana, India.
3. Additional Professor and Co-Guide, Department of General Medicine, Nizam's Institute of Medical Sciences, Hyderabad, Telangana, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Maleha Butul,
6-3-1086/3, Somajiguda, Hyderabad, Telangana, India.
E-mail: butulmaleha67@gmail.com

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