Original Article

Pleiotropic effect of teneligliptin versus glimepiride add-on therapy on hs-CRP and cardiorenal parameters in Indian type 2 diabetes patients: An open-labeled randomized controlled trial

Kanimozhi M, Manisha Bisht[1], Ravikant[2], Arkapal Bandyopadhyay[3], Manisha Naithani[4], Shailendra Handu[5]

MD Pharmacology Resident, [1]Additional Professor, Department of Pharmacology, [2]Professor and Head, Department of Medicine, [4]Professor, Department of Biochemistry, [5]Professor and Head, Department of Pharmacology All India Institute of Medical Sciences, Virbhadra Road, Rishikesh, Uttarakhand, [3]Assistant Professor, Department of Pharmacology, All India Institute of Medical Sciences, Basantapur, Kalyani, West Bengal, India

Abstract

Objective: The objective of the study was to estimate the pleiotropic effect of teneligliptin on high-sensitivity C-reactive protein (hs-CRP) levels and some cardiorenal parameters in comparison to glimepiride, both as add-on therapy to metformin.

Methodology: This 12-week open-label, parallel-group, randomized controlled trial was conducted among Indian people with type 2 diabetes mellitus and on metformin monotherapy with poor glycemic control (glycated hemoglobin >7% or 53 mmol/mol). The endpoints were mean change in hs-CRP levels, systolic blood pressure (SBP), diastolic blood pressure (DBP), serum creatinine, blood urea, estimated glomerular filtration rate (eGFR), and change in cardiovascular (CV) risk categories from baseline to end of 12 weeks.

Results: Seventy participants were randomized (1:1) to receive either teneligliptin 20 mg once daily ($n = 35$) or glimepiride 1 mg twice daily (BD) ($n = 35$) as an add-on to metformin 500 mg BD. The mean age of the participants was 50.65 and 50.7 years in arms 1 and 2, respectively. At 12-weeks end, teneligliptin add-on caused a statistically significant reduction in hs-CRP compared to glimepiride in both per-protocol (PP) and intention-to-treat (ITT) sets. No significant difference was observed for changes in SBP and DBP, creatinine, urea, eGFR levels, and CV risk category in both PP and ITT sets.

Conclusion: Teneligliptin add-on resulted in favorable effects on hs-CRP levels and comparable effects on cardiorenal parameters compared to glimepiride add-on therapy at 12-weeks end.

This trial has been prospectively registered in CTRI (Clinical Trials Registry of India). Registration number: CTRI/2021/08/035342.

Keywords: Dipeptidyl peptidase-4 inhibitors, glimepiride, high-sensitivity C-reactive protein, pleiotropic effects, teneligliptin, type 2 diabetes

Address for correspondence: Dr. Manisha Bisht, Department of Pharmacology, All India Institute of Medical Sciences, Virbhadra Road, Rishikesh - 249 203, Uttarakhand, India.
E-mail: manishabisht@yahoo.co.in

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INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder characterized by inappropriately high glucose concentrations in the blood.[1] The prevalence of diabetes is rising annually at a higher rate, and India is expected to be in the second position next to China, with nearly 134 million people being diagnosed with diabetes mellitus by 2045.[2] Diabetes Mellitus and related complications contributed to approximately 3.1% of total deaths and 2.2% disability-adjusted life years in India as of the year 2016.[3]

Persistently elevated blood glucose levels over time cause irreversible damage to blood vessels in the heart, kidney, retina, and nerves, which present as micro- and macrovascular complications.[4] Cardiovascular (CV) problems affect up to 80% of persons with type 2 diabetes, accounting for around 65% of deaths in this population.[5] Furthermore, CV problems occur one to two decades sooner in diabetes compared to nondiabetes populations.[6]

In recent decades, "chronic low-grade systemic inflammation," also known as "meta-inflammation," has been recognized as an accelerating pathogenic mechanism behind the initiation and progression of diabetes-related complications.[7] hs-CRP is a high sensitivity C-reactive protein assay with a sensitivity range of 0.01–10 mg/L. Such high-sensitivity assays will help in detecting chronic low-grade systemic inflammation,[8] and various studies have concluded that hs-CRP can be an independent predictor of CV diseases (CVDs).[9,10]

Metformin has been approved as a first-line agent for type 2 diabetes treatment, and the choice of second-line agents is individualized. Antidiabetic agents with pleiotropic effects on this chronic inflammation could improve outcomes in these patients and be the better second-line agents of choice.[7] Dipeptidyl peptidase-4 (DPP4) inhibitors are known to have pleiotropic effects owing to the inhibition of soluble DPP4 enzyme, a pro-inflammatory cytokine.[11-14] Albeit, some earlier studies have demonstrated the pleiotropic effects of some DPP4 inhibitors, teneligliptin's effect on hs-CRP is still controversial.[12,13,15] Furthermore, teneligliptin has added advantages of potent DPP4 inhibition, minimal drug–drug interactions, not requiring dose modification in renal and hepatic diseases, and is most cost-effective.[16-18]

Glimepiride is the most potent, safe, long-acting, and relatively CV neutral sulfonylurea.[19] It is evident from previous studies that glimepiride also possesses pleiotropic effects such as anti-inflammatory and antiangiogenic to some extent,[19,20] and it is the second-most commonly prescribed add-on drug to metformin in Indian settings.

Hence, in this study, we assessed the pleiotropic effect of teneligliptin versus glimepiride add-on therapy on hs-CRP and some cardiorenal parameters such as blood pressure (BP), serum creatinine, blood urea, estimated glomerular filtration rate (eGFR), and hs-CRP-based CV risk category predictions.

RESEARCH METHODOLOGY

Research design

This was a 12-week, single-center, open-label, parallel group, randomized (1:1) controlled trial conducted between September 2021 and March 2023 in a tertiary care hospital in Northern India.

Study participants

This study included type 2 diabetes mellitus patients of both genders and ages 18–60 years, who were on metformin monotherapy (1000 mg/day) with poor glycemic control (glycated hemoglobin [HbA1c] >7% or 53 mmol/mol). Participants with type 2 diabetes who were already on insulin or any other incretin-based therapy or any hypoglycemic agents were excluded from the study. Participants with baseline CRP >10 mg/L; any history of acute infection/inflammation; chronic inflammatory conditions, autoimmune diseases, and neoplasia; and serious macrovascular complications (acute myocardial infarction, angina, or stroke) within 6 months of enrolment were also excluded. Participants with type 1 diabetes or any other form of diabetes and pregnant or breastfeeding females were not included in the study.

Randomization and allocation concealment

Randomization was done with computer-generated random numbers generated using Random allocation software 2.0.[21] Block randomization in 1:1 ratio with a block size of four was done. Each random number was kept in an opaque, sealed envelope and opened only at the time of enrollment of the study subjects. Randomization, enrollment, and assignment to intervention were done by one of the coinvestigators.

Sample size calculation

Sample size calculation was done using OpenEpi software.[22] The mean change in hs-CRP was considered for sample size calculation. Based on previous studies[23] (delta was taken as 1.25 and effect size 1.1), it was estimated that 25 participants were needed in each group to achieve 80% power and to detect significant difference between two arms at a 5% significance level. Considering the 10%

dropout rate, it was planned to include 30 participants in each arm. In the present study, a total of 70 participants were included, and 54 participants completed the study at 12-week end.

Study treatment

After block randomization, eligible participants were randomly assigned in 1:1 ratio to either receive tablet teneligliptin 20 mg once daily or tablet glimepiride 1 mg BD as an add-on therapy to tablet metformin 500 mg BD. The included participants were followed up for a period of 12 weeks through weekly telephone calls, and personal visits were made at 0 and 12 weeks.

Endpoints

The primary endpoint of the trial was to estimate the change in mean hs-CRP levels from baseline to the end of 12 weeks, and the secondary endpoints were to estimate the change in mean systolic and diastolic BP (SBP and DBP), serum creatinine, blood urea, eGFR, and change in CV risk category from baseline to 12-week end. To eliminate confounding effects, an exploratory subgroup analysis was done only for per-protocol (PP) set for change in hs-CRP levels and changes in SBP and DBP. The correlation of study variables and hs-CRP was also performed as an ancillary endpoint in the teneligliptin arm. The other secondary endpoints were mean change in HbA1c, fasting blood sugar, and postprandial blood sugar at 12-week end (results not reported). The safety and tolerability of study drugs were also evaluated in both groups.

Evaluation methods

Estimation of hs-CRP was done by enzyme-linked immunosorbent assay; eGFR was calculated as one of the measures of kidney function using modification of diet in renal disease s equation.[24]

Previous research has proven that even a slight increase in hs-CRP levels is related to an increased risk of significant CV events in future. In this study, participants in PP set were categorized into different CV risk categories based on their hs-CRP levels as follows: participants with hs-CRP levels of <1.0 mg/L were categorized as low CV risk, 1.0–3.0 mg/L as average CV risk, and 3.0–10.0 mg/L as high CV risk.[25]

Statistical analysis

Statistical analysis was done using the Statistical Package for the Social Sciences (SPSS version 25). Participant characteristics were summarized as means and standard deviations (X ± SD) for continuous variables and as frequencies and percentages for categorical variables. Both PP and intention-to-treat (ITT) analysis were performed for primary and secondary endpoint analysis. After checking for normality of data using the Shapiro–Wilk test, paired *t*-test and Student's *t*-test were applied to analyze the changes in mean hs-CRP, BP, creatinine, urea, and eGFR levels from baseline to 12-week end within the group and between the group, respectively. For categorical data, the Chi-square test was applied to find the statistical significance. $P \leq 0.05$ was considered statistically significant for all statistical analyses. Pearson's and Spearman's correlation tests were used to analyze the correlation between study variables.

Ethical conduct of study

This trial was implemented in full compliance with the protocol and principles of the "Declaration of Helsinki," Good Clinical Practice, and New Drugs and Clinical Trials rules 2019, India. This trial was prospectively registered under CTRI-INDIA (Trial number: CTRI/2021/08/035342) and approved by the institutional ethics committee. The patients were enrolled after baseline screening and obtaining written informed consent. Confidentiality of the information obtained from the patient was maintained, and the identity of the patient was not revealed anywhere.

RESULTS

After screening 194 participants for eligibility, 72 participants were enrolled in the trial. Blood samples were collected for baseline assessments before drug intervention. Two participants had high baseline hs-CRP (>10 mg/dL), and thus, they were excluded from the study. Out of 70 participants who received the intended intervention, 54 (77.14%) completed the study at the 12-week end. Thus, 54 participants were included for PP analysis, and 70 participants who received the study drug were included for ITT analysis. The CONSORT flowchart is depicted in Figure 1.

Baseline demographic, lab parameters, and clinical characteristics were comparable between the two treatment arms without any statistical difference ($P > 0.05$), as depicted in Table 1. The antihypertensive medications included drugs from the following classes: angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and calcium channel blockers.

Effects on high-sensitivity C-reactive protein levels

Both teneligliptin and glimepiride add-on caused a significant reduction in hs-CRP levels at the 12-week end in both PP and ITT sets [Tables 2 and 3]. On comparing both the arms, teneligliptin add-on resulted in significant

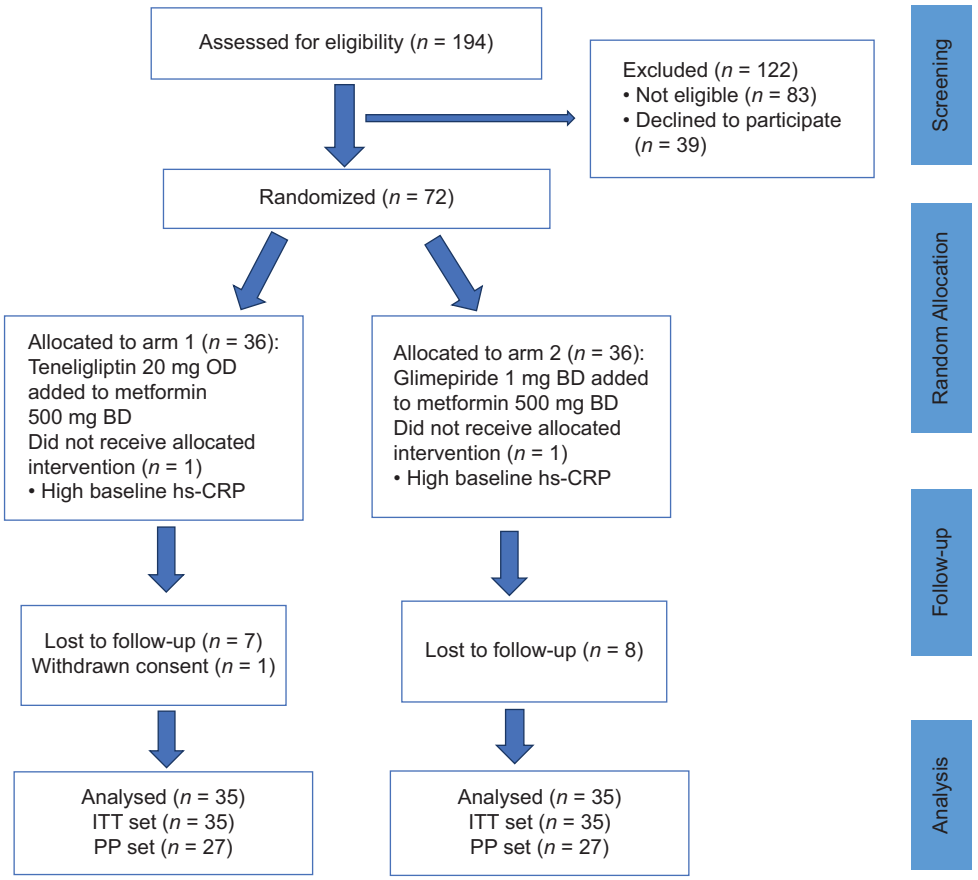

Figure 1: CONSORT flowchart. hs-CRP = High-sensitivity C-reactive protein

hs-CRP reduction more than glimepiride add-on in both PP and ITT set at 12-week end ([PP set: Mean difference (MD): −0.625; 95% confidence interval (CI): −1.22 to −0.023; $P = 0.04$*] [ITT set: MD: −0.625; 95% CI: −1.08 to −0.165; $P = 0.008$*]) [Figure 2a].

In subgroup analysis for participants with statin therapy and without statins therapy, only teneligliptin caused a significant reduction in hs-CRP levels at the 12-week end ([With statins therapy: Teneligliptin ($n = 12$): 2.64 vs. 1.33; $P = 0.002$* and Glimepiride ($n = 6$): 1.88 vs. 1.71; $P = 0.30$] [Without statins therapy: Teneligliptin ($n = 15$): 1.39 vs. 0.80; $P = 0.01$* and Glimepiride ($n = 21$): 1.86 vs. 1.65; $P = 0.08$]). Comparison between interventions showed that there is no statistically significant difference between the teneligliptin arm and glimepiride arm in both subgroups of participants with and without statin therapy.

Effects on systolic blood pressure

In both the PP set and ITT set, the teneligliptin add-on caused a significant reduction in SBP at the 12-week end, and the glimepiride add-on did not cause a significant effect on SBP at the 12-week end [Tables 2 and 3]. On comparing the two arms, no significant difference was observed between them in both PP and ITT set at the 12-week end ($P = 0.06$) [Figure 2b].

In a subgroup analysis for participants not on antihypertensive medications, only teneligliptin caused a significant reduction in SBP at the 12-week end (teneligliptin [$n = 21$]: 130.95 vs. 128.33; $P = 0.001$* and glimepiride [$n = 19$]: 135.47 vs. 134.52; $P = 0.43$). On comparing the two arms, no significant difference was observed at the 12-week end ($P = 0.21$).

Effects on diastolic blood pressure

In both the PP set and ITT set, the teneligliptin add-on caused a significant reduction in DBP at the 12-week end, and the glimepiride add-on did not cause a significant effect on DBP at the 12-week end [Tables 2 and 3]. On comparing the two arms, no significant difference was observed between them in both PP and ITT set at the 12-week end.

In a subgroup analysis for participants not on antihypertensive medications, both teneligliptin and glimepiride add-on did not cause significant effects on DBP at the 12-week end [(teneligliptin: 78.14 vs. 76.90; $P = 0.13$; $n = 21$) (glimepiride: 76.42 vs. 76; $P = 0.58$; $n = 19$)]. On comparing the two arms, no significant difference was observed at the 12-week end ($P = 0.75$).

Table 1: Baseline demographic characteristics

Study variables	Arm 1 (teneligliptin + metformin) (*n*=35)	Arm 2 (glimepiride + metformin) (*n*=35)	*P*
Age (years)*	50.65 (7.36)	50.7 (6.38)	0.94
Gender			
Males	15 (42.8)	19 (54.2)	0.33
Females	20 (57.1)	16 (45.7)	
Duration of diabetes (years)*	2.67 (1.51)	2.31 (1.44)	0.30
Anthropometric measurements			
Body weight (kg)*	66.53 (11.19)	68.58 (10.42)	0.43
Height (cm)*	160.47 (6.75)	160.25 (7.61)	0.90
Blood pressure (mmHg)			
SBP*	135.65 (15.5)	137.97 (18.57)	0.57
DBP*	79.08 (9.23)	78.82 (11.26)	0.91
Diabetic complications			
Diabetic nephropathy	4 (11.42)	2 (5.71)	0.39
Diabetic neuropathy	15 (43)	18 (51.43)	0.47
Diabetic retinopathy	3 (8.57)	2 (5.71)	0.64
CVD/events	4 (11.42)	3 (8.57)	0.69
Co-morbidities			
Hypertension	13 (37.14)	14 (40)	0.62
Dyslipidemia	23 (65.71)	19 (54.28)	0.32
Hypothyroidism	5 (14.28)	4 (11.42)	0.72
Concomitant medications			
Antihypertensives	13 (37.14)	10 (28.57)	0.44
Statins	15 (42.85)	9 (25.71)	0.13
Aspirin and clopidogrel	4 (11.42)	2 (5.71)	0.39
Others	23 (65.71)	16 (45.71)	0.09
Biochemical parameters			
HbA1C* (%)	8.66 (1.6)	8.78 (1.8)	0.77
hsCRP* (mg/dL)	1.87 (1.9)	1.90 (1.4)	0.95
Serum creatinine* (mg/dL)	0.82 (0.28)	0.75 (0.19)	0.21
Blood urea* (mg/dL)	31.82 (9.8)	29.07 (6.4)	0.17
Derived parameters			
eGFR* (mL/min/1.73 m^2)	101.80 (25.4)	109.22 (29)	0.26

*Values mentioned as mean (SD) and *P* value for these values obtained by Student's *t*-test. Categorical values are mentioned as frequency (proportions) (*n* [%]) and *P* value for these was obtained using the Chi-square test. SBP=Systolic blood pressure, DBP=Diastolic blood pressure, hs-CRP=High-sensitivity C-reactive protein, eGFR=Estimated glomerular filtration rate, HbA1C=Glycated hemoglobin, CVD=Cardiovascular diseases

Table 2: Change in primary endpoints from baseline to the end of 12 weeks for per-protocol set (*n*=27 in each arm)

Parameters	Teneligliptin arm (Arm 1)		*P*	Glimepiride arm (Arm 2)		*P*	*P* value for Arm 1 versus Arm 2
	Baseline	At 12-week		Baseline	At 12-week		
Mean hsCRP (mg/dL)	1.95 (2.01)	1.04 (0.84)	0.001*	1.86 (1.52)	1.66 (1.31)	0.006*	0.04*
Mean SBP (mm/Hg)	133.51 (14.5)	130.33 (14.05)	<0.001*	137.48 (18.8)	136.22 (15.6)	0.15	0.15
Mean DBP (mm/Hg)	78.81 (10)	77.11 (8.25)	0.015*	78.29 (11.5)	77.70 (9.7)	0.32	0.81
Mean serum creatinine (mg/dL)	0.829 (0.28)	0.77 (0.24)	<0.001*	0.75 (0.20)	0.74 (0.16)	0.38	0.60
Mean blood urea (mg/dL)	32.66 (10.7)	30.85 (10.06)	0.001*	29.39 (7.11)	28.70 (5.77)	0.20	0.34
Mean eGFR (mL/min/1.72 m^2)	100.65 (27.4)	104.11 (29)	0.04*	109.11 (30.15)	109.75 (30.2)	0.65	0.48

*$P < 0.05$ statistically significant values. All values are mentioned as mean (SD). In ITT set, missing values were imputed with series mean. ITT set: All patients who have received at least one dose of study treatment. PP set: Patients who completed the study as per protocol. ITT=Intention-to-treat, PP=Per-protocol, SD=Standard deviation, SBP=Systolic blood pressure, DBP=Diastolic blood pressure, hs-CRP=High-sensitivity C-reactive protein, eGFR=Estimated glomerular filtration rate

Table 3: Change in primary endpoints from baseline to the end of 12 weeks for intention-to-treat set (*n*=35 in each arm)

Parameters	Teneligliptin arm (Arm 1)		*P*	Glimepiride arm (Arm 2)		*P*	*P* value for Arm 1 versus Arm 2
	Baseline	At 12-week		Baseline	At 12-week		
Mean hsCRP (mg/dL)	1.87 (1.91)	1.04 (0.73)	0.001*	1.90 (1.4)	1.66 (1.14)	0.050*	0.008*
Mean SBP (mm/Hg)	135.65 (15.5)	130.33 (12.2)	0.002*	137.97 (18.5)	136.22 (13.7)	0.28	0.06
Mean DBP (mm/Hg)	79.08 (9.23)	77.11 (7.22)	0.008*	78.82 (11.2)	77.70 (8.5)	0.25	0.75
Mean serum creatinine (mg/dL)	0.822 (0.28)	0.77 (0.21)	0.053	0.75 (0.19)	0.74 (0.14)	0.70	0.49
Mean blood urea (mg/dL)	31.82 (9.8)	30.85 (8.8)	0.14	29.07 (6.41)	28.70 (5.04)	0.45	0.21
Mean eGFR (mL/min/1.72 m^2)	101.80 (25.4)	104.11 (25.36)	0.23	109.22 (29.05)	109.75 (26.4)	0.82	0.36

*$P < 0.05$ statistically significant values. All values are mentioned as mean (SD). In ITT set, missing values were imputed with series mean. ITT set: All patients who have received at least one dose of study treatment. PP set: Patients who completed the study as per protocol. ITT=Intention-to-treat, PP=Per-protocol, SD=Standard deviation, SBP=Systolic blood pressure, DBP=Diastolic blood pressure, hs-CRP=High-sensitivity C-reactive protein, eGFR=Estimated glomerular filtration rate

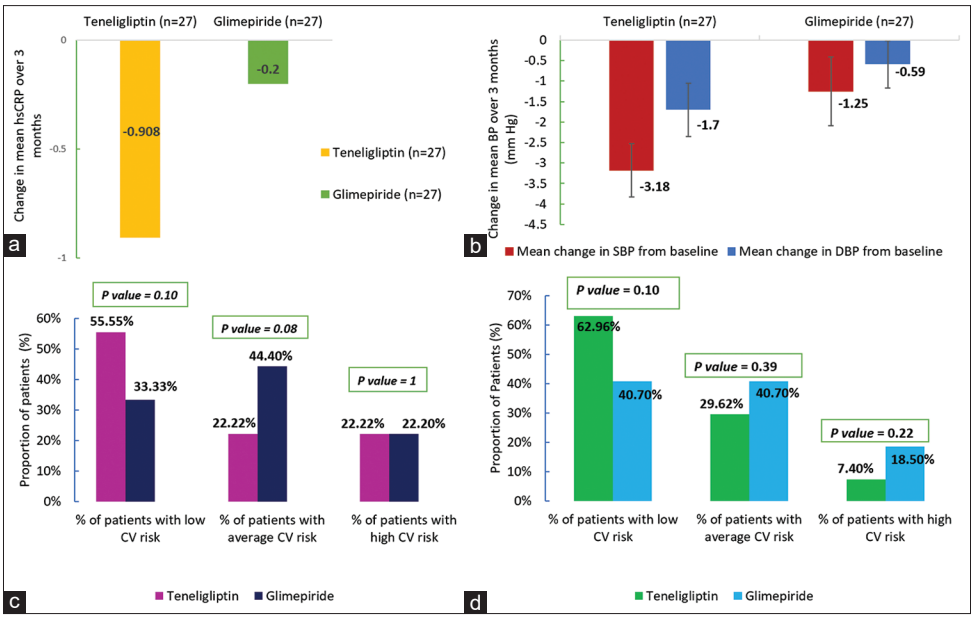

Figure 2: (a) Mean change in high-sensitivity C-reactive protein level from baseline to the end of 12 weeks (per-protocol [PP] set). (b) Mean change in systolic blood pressure and diastolic blood pressure from baseline to the end of 12 weeks (PP set). (c) The proportion of patients in each cardiovascular (CV) risk category at baseline (PP set). (d) The proportion of patients in each CV risk category at the end of 12 weeks (PP set). hs-CRP = High-sensitivity C-reactive protein, CV = Cardiovascular, SBP = Systolic blood pressure, DBP = Diastolic blood pressure

Effects on serum creatinine and blood urea

Teneligliptin add-on in the PP set alone caused a significant reduction in serum creatinine and blood urea levels at 12-week end, but a similar effect was not seen in the ITT set, whereas glimepiride add-on did not cause significant effects in both PP and ITT set at the 12-week end. On comparing the two arms, no significant difference was observed in both PP and ITT set at the 12-week end [Tables 2 and 3].

Effects on estimated glomerular filtration rate

Teneligliptin add-on in the PP set alone caused a significant increase in eGFR values at the 12-week end; however, a similar effect was not seen in the ITT set, whereas glimepiride add-on did not cause significant effects in both PP and ITT set at the 12-week end. On comparing the two arms, no significant difference was observed in both PP and ITT set at the 12-week end [Tables 2 and 3].

Cardiovascular risk categories

At baseline, the proportion of participants in each CV risk category was similar [Figure 2c]. At the 12-week end, teneligliptin arm had a higher proportion of participants in low- and average-risk categories and low numbers in the high-risk category. Whereas in the glimepiride arm, a very small proportion of participants shifted from the high-risk category to low- and average-risk categories. At 12-week end, there is no statistically significant difference between the teneligliptin and glimepiride arm [Figure 2d].

Correlation analysis

In correlation analysis, we found a significant moderate negative correlation ($r = -0.438$; $P = 0.02$*) between the duration of diabetes and Δhs-CRP levels in the teneligliptin arm (PP set). Furthermore, a significant moderate negative correlation was observed between Δhs-CRP levels and previous history of CV events (rho = −0.439; $P = 0.02$*) [Figure 3]. This implies that the decrease in hs-CRP was smaller in participants with a previous history of CV events and longer diabetes duration. We also found a nonsignificant, very weak positive correlation between ΔHbA1c and Δhs-CRP levels ($r = 0.06$).

Safety

The overall occurrence of adverse drug reactions (ADRs) was comparable between both teneligliptin arm and the glimepiride arm (62.85% vs. 68.57%; $P = 0.051$). All the observed ADRs were of mild-to-moderate intensity, with 0 severe ADR incidence in both groups. The most frequently observed ADRs in both groups were weakness, numbness, and insomnia, and the proportion of people experiencing these ADRs was almost similar in both groups. Gastrointestinal-related side effects such as abdominal pain and constipation were the most common ADRs observed in the teneligliptin group.

DISCUSSION

Hs-CRP is a principal biomarker of chronic low-grade systemic inflammation and plays a vital role in atherosclerotic

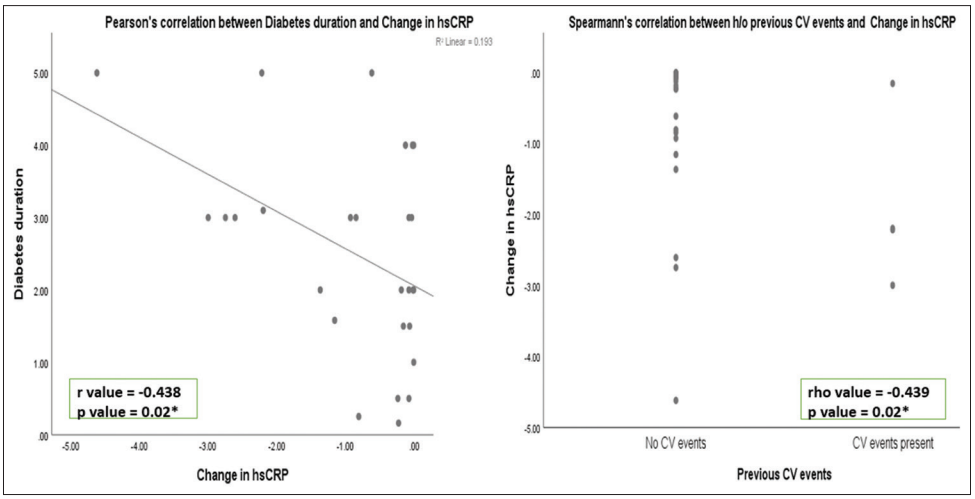

Figure 3: Scatter plot for correlation analysis of high-sensitivity C-reactive protein with other study variables. CV = Cardiovascular, hs-CRP = High-sensitivity C-reactive protein

plaque formation along with low-density lipoprotein cholesterol.[10,12] Therefore, it can serve as a surrogate marker for the prediction of CVD risk in type 2 diabetes patients. In this study, we compared the effects of two commonly prescribed second-line drugs in Indian settings, teneligliptin and glimepiride add-on therapy on, hs-CRP, and some cardiorenal parameters.

At 12-week end, both teneligliptin and glimepiride add-on resulted in a significant decrease in hs-CRP levels in the PP and ITT set, but when compared between the groups, teneligliptin caused a more significant decrease in hs-CRP levels than glimepiride in both PP and ITT set. Syngle *et al.* and Butul *et al.* also reported a similar decrease in hs-CRP levels with teneligliptin and glimepiride therapies.[26,27] The results were consistent across subgroups of participants with statins and without statins treatment in the teneligliptin arm alone, and this confirms the pleiotropic effect of teneligliptin on hs-CRP. The possible reason for hs-CRP reduction in the glimepiride arm was due to the use of background medications as consistent results were not observed in subgroup analysis.

The link between hs-CRP levels and future risk of major adverse CV events was well established by previous researches.[25,28] At the 12-week end, both teneligliptin and glimepiride use resulted in clinically significant improvement in CV risk categories.

In correlation analysis, we found that the decrease in hs-CRP levels was less if the participant had a previous history of CV events. This implies that it is difficult to reverse the inflammatory process progression once it has occurred. We also found nonsignificant, very weak positive correlation between ΔHbA1c and Δhs-CRP levels. The nonsignificance in this correlation might be attributed to the smaller sample size in our study. This finding possibly shows that improvement in glycemic control and insulin sensitivity might be one of the possible mechanisms behind the pleiotropic effects of teneligliptin on hs-CRP. However, further studies are needed to confirm this.

At the 12-week end, only teneligliptin add-on in the PP set resulted in significant favorable effects on SBP and DBP, and no significant difference was observed in comparing the teneligliptin and glimepiride add-on. Takamiya *et al.* also reported a decrease in SBP and DBP with teneligliptin use at 3 months end, but the decrease was less compared to our study. A possible explanation could be the monotherapy in Takamiya *et al.*, whereas in our study, it was add-on therapy.[29] Syngle *et al.* reported a similar decrease in DBP as that of our study findings.[27]

From previous studies, it was known that teneligliptin causes a modest decrease in both SBP and DBP compared to placebo, but a similar decrease compared to other antidiabetic drugs,[30] and our study results confirm these findings. In a subgroup analysis on participants not taking antihypertensive drugs, a significant decrease in SBP was observed only in the teneligliptin arm, which further confirms its consistent pleiotropic effects. The possible mechanism behind this effect could be an improvement in insulin sensitivity, suppression of sympathetic activity, and natriuretic action of incretins.[29]

Only the addition of teneligliptin to the PP set had substantial positive effects on creatinine, urea, and eGFR levels at the end of the 12-week period; there was no significant difference between the teneligliptin and glimepiride add-on therapy. Kumar and Syngle *et al.*

reported similar effects on creatinine levels as that of our study,[27,31] whereas our study results contradict the findings reported by Kiran *et al*. and Shah for effects on urea and eGFR, respectively.[32,33] The possible reason for this difference could be the inclusion of all stages of renal function in our study.

Teneligliptin's potential mode of action for its reno-protective properties has been suggested as oxidative stress attenuation.[34] As the assessment of teneligliptin's effect on oxidative stress was beyond the scope of this study, this possible mechanism for positive effects on renal parameters (serum creatinine, blood urea, and eGFR) could not be elucidated in our study.

In this study, approximately 62.85% of participants in the teneligliptin arm and 68.57% of participants in the glimepiride arm experienced ADRs, which were elicited with the help of the ADR checklist. All the ADRs observed were mild to moderate in severity, and no hospitalization was done for the management of these ADRs. Similar results were reported by Werida *et al*.,[35] who compared vildagliptin (another DPP4 inhibitor) with glimepiride.

Strength and limitations

This study has successfully explored the pleiotropic effects of teneligliptin versus glimepiride add-on to metformin monotherapy on hs-CRP and some cardiorenal parameters. We performed both ITT and PP analysis to preserve the randomization effects, sample size, and power and also assessed the effect of receiving the drug. However, there are some limitations, such as short duration, which hindered the assessment of long-term effects of teneligliptin on inflammatory biomarkers and exploration of the association between changes in hs-CRP levels and CVD occurrence; treatment effects on other inflammatory biomarkers such as tumor necrosis factor-alpha and IL-6 were not studied. Evaluation of their effects could have added some more insights into the pleiotropic effects of teneligliptin.

CONCLUSION

Teneligliptin add-on resulted in more favorable effects on hs-CRP, BP levels, and renal parameters compared to glimepiride add-on; however, further long-duration studies are needed to confirm its pleiotropic benefits.

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Conflicts of interest

There are no conflicts of interest.

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