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Effect of Teneligliptin-metformin Combination Therapy on Glycemic Control in Indian Patients: A Prospective Comparative Clinical Study

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Abstract

Aim: To compare the effectiveness of teneligliptin/ metformin as monotherapies with teneligliptin-metformin combination therapies in an Indian setting. *Patients and Methods*: The prospective observational study included 207 subjects aged >40 years with suboptimal control of T2DM (glycated hemoglobin (HbA1c) >7.5%). The subjects were categorized into the following three groups based on the treatment received: 63 (30.4%) in group 1 received 20 mg of teneligliptin and metformin SR (500 mg) as individual therapies, 76 (36.7%) in group 2 were managed with 1000 mg metformin and 20 mg of teneligliptin in combination, and 68 subjects (32.9%) in group 3 received 500 mg metformin and 20 mg of teneligliptin in combination. HbA1c, FGS, and PPBG were measured for all the participants at baseline and after the administration of drugs (HbA1c at 12 weeks, and FGS and PPBG at 4 and 12 weeks). Anthropometric and laboratory parameters were compared by ANOVA for normal data, Kruskal Wallis for not normal data and *chi*-square test for counts data. *Results:* The mean age of patients was 53.94 ± 10.64 years with a male-to-female ratio of 1:0.76. Comparisons of all the variables between baseline and 12th week were found to be highly significant across the three groups and further t-test analysis also corroborated the findings (P<0.001). Percentage changes showed that the overall effects of the drugs in reducing HbA1c, FGS and PPBS were more prominent in the group 3 followed by group 2 and 1. *Conclusion:* Combined pill metformin (500 mg)-teneligliptin (20 mg) may serve as effective alternative to metformin/teneligliptin individual therapies, thereby to reduce the pill burden and improve patient compliance in an Indian setting.

Keywords: Metformin; Teneligliptin; Diabetes; T2DM; Glycemic control.

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Introduction

Despite the launching of the National Program for Prevention and Control of Cancer, Diabetes, Cardiovascular Diseases, and Stroke (NPCDCS) in 2010 by Government of India, recent estimates show an alarming increase in the prevalence of diabetes in the country. This could be attributed to weaker adoption of the national program and unavailability of treatment to chronic patients, especially in the rural regions of India.[1]As per the reports of International Diabetes Federation, 82 million people are suffering from diabetes in India and it is estimated to reach 151 million by 2045.[2] The Global Burden of Disease Study has reported that the number of diabetes patients in India has increased from 26 million in 1990 to 65 million in 2016.[3]

The guidelines from American Diabetes Association (ADA), American Association of Clinical Endocrinologists and American College of Endocrinology in 2016 have recommended the use of dipeptidyl peptidase 4 (DPP-4) inhibitors as first-or second-line agents for managing diabetes.[4] Teneligliptin, a recently developed oral dipeptidyl peptidase 4 (DPP-4) inhibitor, has been reported to confer persistent reduction in HbA1c of 0.8%–0.9% within 3 months of treatment. The long-lasting

glucose-lower effects are contributed by the unique 'J-shaped' structure of teneligliptin, formed by five consecutive rings. A comparative study carried out by Tintu et al. in Indian T2DM patients has demonstrated that teneligliptin in combination with metformin is a cost-effective alternative than other gliptins in significantly improving the glycemic parameters and it can be used without any dose adjustments in patients with hepatic or renal impairments. The other advantages of the combination therapy noted by the researchers are convenient once daily administration, longer half-life of 26.9 hours, and dual–mode of elimination via renal and hepatic routes.[5] Literature evidence also substantiates the effectiveness and safety of teneligliptin an add-on to metformin treatment in T2DM patients.[6] Studies indicate that metformin acts by decreasing Fasting Glucose Sugar (FGS), where DPP-4 mainly focuses on the inhibition of and Postprandial Blood Glucose (PPBG).[4]

Although teneligliptin is a widely prescribed DPP4-inhibitor in India, there is a lack of data regarding teneligliptin monotherapy and in combination with metformin in patients with newly diagnosed T2DM, especially from the southern part of the country.[4] The present study is intended to compare the effectiveness of teneligliptin and metformin as monotherapies with tenegliptin-metformin (55 mg/10000 mg) combination therapies in an Indian setting.

Patients and Methods

The prospective comparative study included subjects aged >40 years with suboptimal control of T2DM (glycated hemoglobin (HbA1c) >7.5%), despite following a good exercise and dietary plan to manage blood glucose levels. The study was approved by the institutional ethics committee and informed consent was obtained from all the participants. The inclusion and exclusion criteria considered were as follows:

Inclusion Criteria

Subjects aged between from 40-70 years of either sex.

Those with glycated hemoglobin (HbA1c) >7.5%.

Patients with the ability to understand and provide written informed consent form.

Exclusion Criteria

Pregnant/lactating women

Subjects with T1DM or those having complications associated with diabetes (nephropathy, ketoacidosis, coma, hyperosmolar state, retinopathy, neuropathy etc).

Patients with known hypersensitivity to any components of the formulation.

Those who had taken any oral antihyperglycemic drugs 8 weeks prior to screening

Those who had received insulin within 12 weeks of screening. Patients receiving systemic corticosteroids.

The study participants were categorized into the following three groups based on the drugs and dosages received: Group 1 was managed with teneligliptin 20 mg Sustained Release (SR) and metform in SR (500 mg) as individual therapies in the morning, group 2 with metform in (1000 mg) and teneligliptin (20 mg) SR combination therapy, and group 3 with met form in (500 mg) and teneligliptin (20 mg) SR combination therapy. HbA1c, FGS, and PPBG for all the study diabetic patients were recorded before (baseline) and after the administration of drugs (HbA1cat 12 weeks, and FGS and PPBG at 4 and 12 weeks). FGS and PPBG levels were measured using hexokinase method, and glycated hemoglobin (HbA1c) levels using turbidimetric inhibition immunoassay (TINIA) with a reference range of 4.2 – 21% (Cobas c 111 by Roche Diagnostics India Pvt. Ltd). The outcome measures considered wereFBG, PPBG and HbA1c over time from baseline.

Statistics

Statistical analyzes were performed using R statistical software version 3.6.1. Statistical measures obtained included descriptive, box plots, proportions, mean and standard deviations. Data were collected and analysedfor the patients satisfying the inclusion and exclusion criteria. Results were presented as descriptive statistics in the form of mean/ proportion, and percentage, and possible associations were derived by using suitable parametric and non-parametric tests of significance. Comparison of anthropometric and laboratory parameters by ANOVA for normal data, Kruskal Wallis for not normal data and *chi*-square test for counts data. $P < 0.05$ was considered statistically significant for all analyzis. Results were presented as Tables, Charts and Figures as applicable.

Results

The study included 207 patients with inadequately controlled T2DM, as per the HbA1c status. The mean age of patients was 53.94 ± 10.64 years with a male-to-female ratio of 1:0.76. The corresponding number of subjects belonging to the three groups and the treatments received were as follows: 63(30.4%) patients of group 1 received 20mg of teneligliptinand metformin SR (500mg) as individual the rapies, 76(36.7%) in group 2 were managed with 1000 mg metformin and 20mg of teneligliptin in combination, and 68 subjects (32.9%) in group 3 received 500 mg metformin and 20 mg of teneligliptin in combination

Table 1: Demographic characteristics and categorization of the study subjects.

Parameters		Results
Gender	Female	90(43.5%)
	Male	117(56.5%)
Age		53.94±10.64
Group 1	Teneligliptin 20mg and metformin SR (500 mg) as individual therapies	63(30.4%)
Group 2	Metformin (1000mg)-teneligliptin (20mg) combination	76(36.7%)
Group 3	Metformin (500mg)-teneligliptin (20mg)	68(32.9%)

Group-wise comparisons for HbA1c, FGS and PPBG were carried out for group1, 2 and 3 (Table 2). The mean baseline values for HbA1c noted for the corresponding groups were 8.27 ± 1.38%, 8.57 ± 1.53% and 8.69± 1.90% and the respective values noted at 12th week were 7.19 ± 0.90%, 7.23 ± 0.77% and 7.19 ± 0.72% (Table 2). FGS mean baseline values noted for group 1, 2 and 3 were 171.32 ±62.21, 191.95 ± 81.21 and 175.99 ± 66.64 respectively. The corresponding values noted at the 4th week were 138.27 ±31.17, 155.16 ± 51.30, and141.51 ± 43.66,and at the12th week were 125.52 ±27.74, 131.96 ± 32.85 and 123.19 ± 31.96 (Table 2). The PPBG mean baseline values noted for group 1, 2 and 3 at baseline were 238.16 ±88.49, 249.80 ± 86.97 and 249.59 ± 98.26. The respective values noted across the groups at 4th week were 197.46 ±54.90, 197.64 ± 63.57 and 193.82±54, and at 12th week were 169.59 ±44.29, 170.33 ± 47.96 and 166.74 ± 34.01 respectively (Table 2). Comparisons of the HbA1c, FPG and PPBG values between baseline and 12th week were found to be highly significant across the three groups and further t-test analyis also corroborated the findings (Table 2).

Change in HbA1c noted for groups 1, 2 and 3 were –1.08±1.13, –1.34±1.09 and –1.5±1.41 respectively. The percent changes in HbA1c observed at the end of 12 week for the respective groups were 13.1%, 15.6% and 17.3% (Fig.1). Changes in FGS found at the end of 4th week for groups 1, 2 and 3 were –33.05±55.59, –36.79±71.39 and –34.47±59.88 respectively, and the percent changes calculated for the corresponding groups were 19.3%, 19.2% and 19.6% (Fig.2). Changes in FGS at the end of 12th week were –45.79±54.34, –59.99±73.89 and –52.79±61.31, and the percent changes noted for the same were 26.7%, 31.3%, and 30.0% respectively (Fig.3). Changes in PPBS at the end of 4th week

Table 2 : Comparison of study variables across the three groups.

Parameters		Group 1 (n= 63)	Group 2 (n= 76)	Group 3 (n= 68)
HbA1c (%)	Baseline	8.27 ± 1.38	8.57 ± 1.53	8.69 ± 1.90
	12 weeks	7.19 ± 0.90	7.23 ± 0.77	7.19 ± 0.72
P-value		<0.001	<0.001	<0.001
FPG (mgdL^{-1})	Baseline	171.32 ±62.21^{a†}	191.95 ± 81.21^{a}	175.99 ± 66.64^{a}
	4 weeks	138.27 ±31.17^{b}	155.16 ± 51.30^{b}	141.51 ± 43.66^{b}
	12 weeks	125.52 ±27.74^{c}	131.96 ± 32.85^{c}	123.19 ± 31.96^{c}
P-value		<0.001	<0.001	<0.001
PPBS(mgdL^{-1})	Baseline	238.16 ±88.49^{a}	249.80 ± 86.97^{a}	249.59 ± 98.26^{a}
	4 weeks	197.46 ±54.90^{b}	197.64 ± 63.57^{b}	193.82 ±54.11^{b}
	12 weeks	169.59 ±44.29^{c}	170.33 ± 47.96^{c}	166.74 ± 34.01^{c}
P-value		<0.001	<0.001	<0.001

† different superscripts across the column for each parameter are statistically different from each other at p value <0.005 for t-test.

were –40.7±77.2, –52.16±74.96 and –55.76±78.62 (Fig. 4), and the corresponding percent changes calculated were 17.1%, 20.9% and 22.3%. Changes in PPBS at the end of 12th week were –68.57±80.08, –79.47±78.88 and –82.85±86.3for group 1, 2 and 3 respectively (Fig. 5), and the corresponding percent changesnoted were 28.8%, 31.8%, and 33.2%. These percentage changes showed that the overall effects of the drugs in reducing HbA1c, FGS and PPBS were more prominent in the group 3 followed by group 2 and 1, though the findings were statistically not significant.

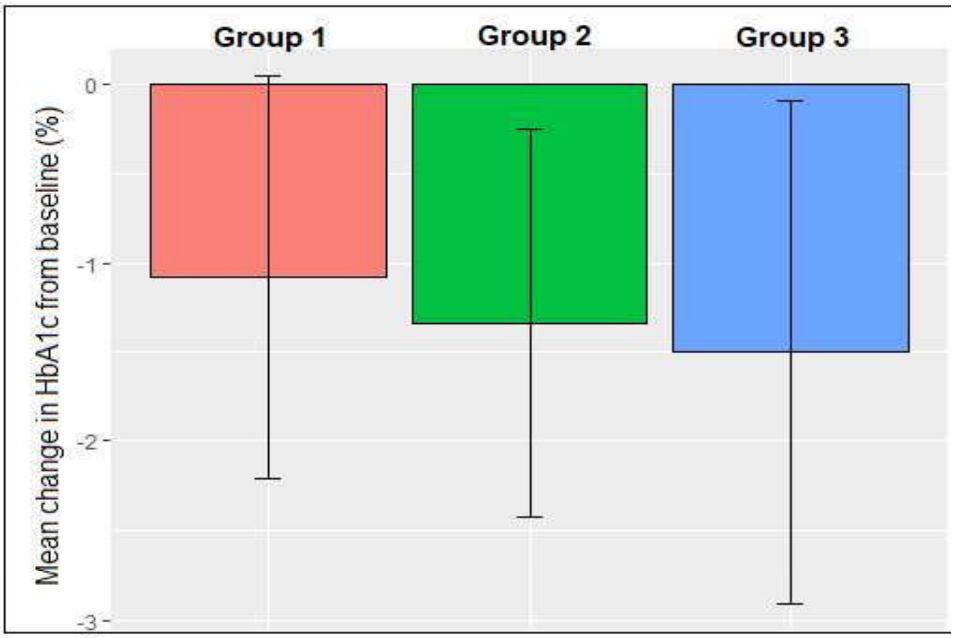

Fig. 1: Changes in HbA1c at week 12 from baseline (mean [SD]).

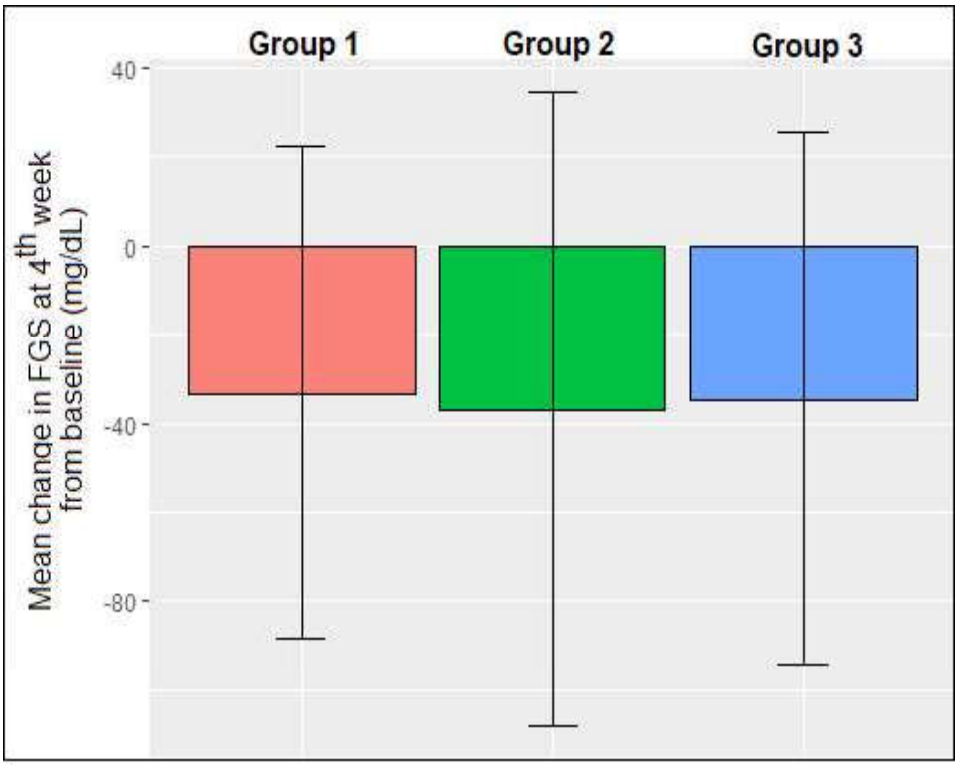

Fig. 2: Changes in FGS at week 4 from baseline (mean [SD]).

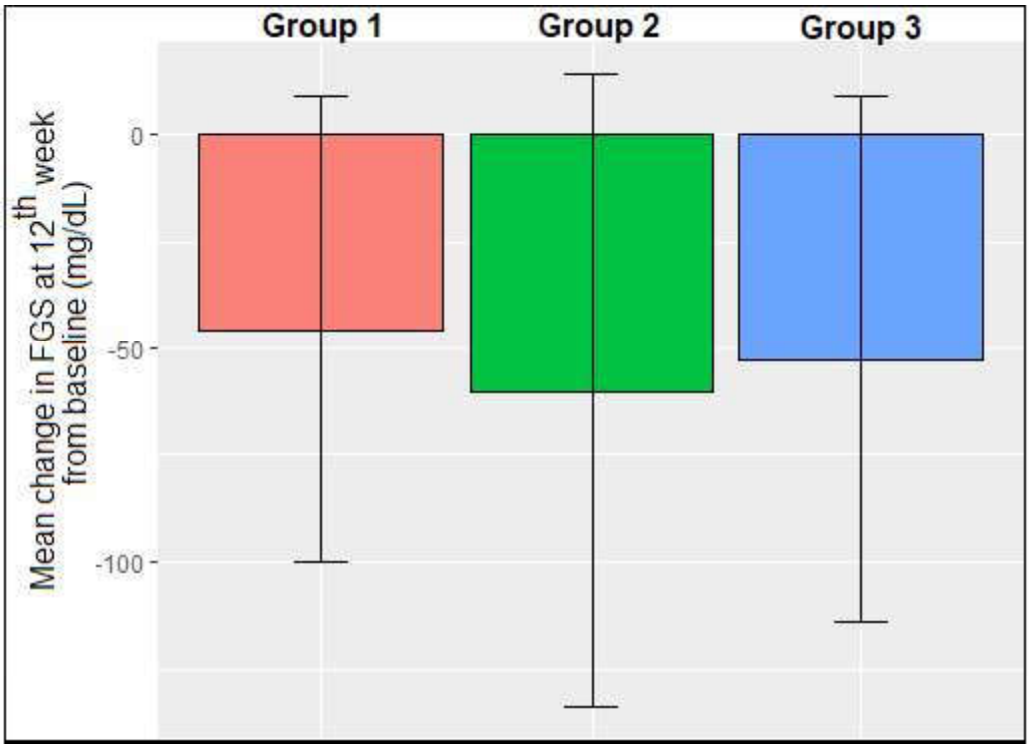

Fig. 3: Changesin FGS at week 12 from baseline (mean [SD]).

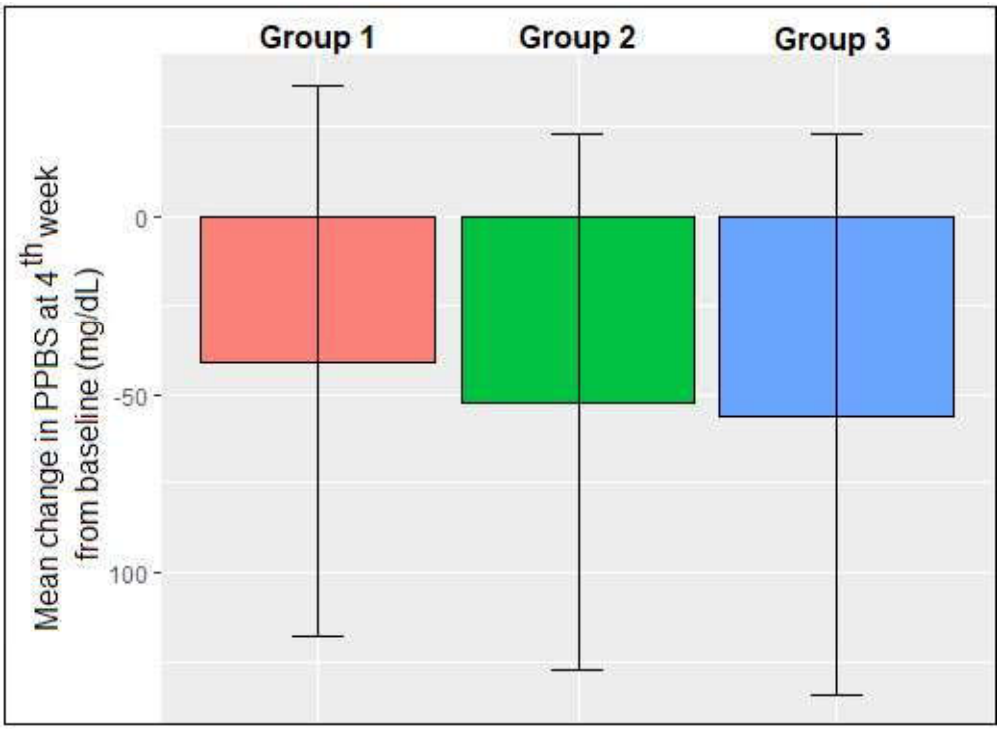

Fig. 4: Changesat week 4 in PPBS from baseline (mean [SD]).

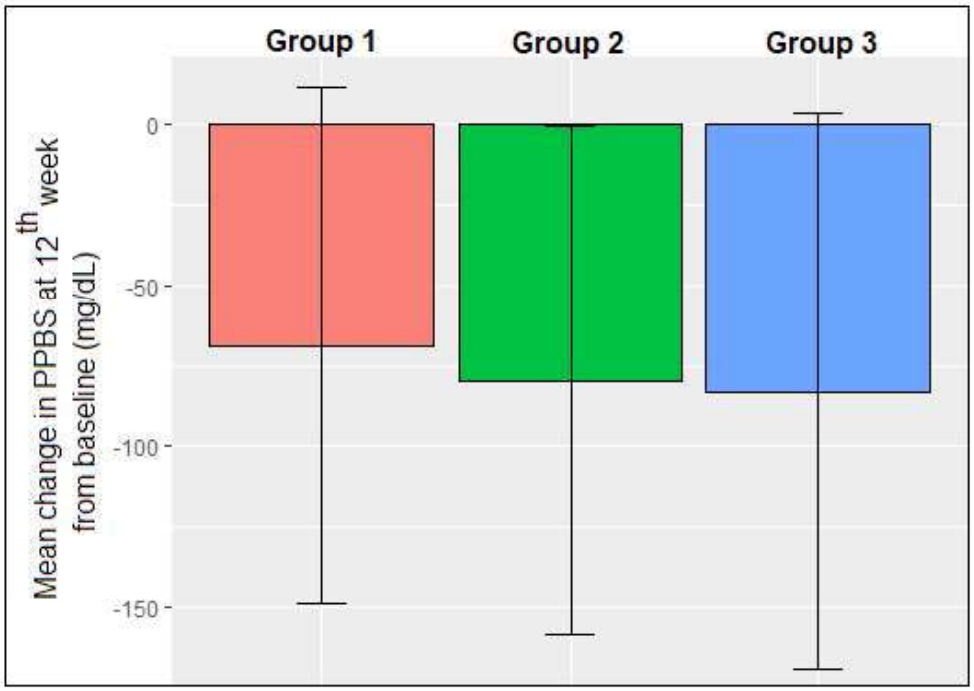

Fig. 5: Changes in PPBS at week 12 from baseline (mean [SD]).

Discussion

The present study has demonstrated that the three regimens used have comparable effectiveness in significantly reducing the HbA1c, FPG and PPBS. These results validate the potential of teneligliptin/ metformin mono and combination therapies in improving the glycemic parameters in Indian patients with T2DM. Though statistically not significant, the overall effects of the teneligliptin and metformin 500 mg combination therapy in reducing HbA1c, FGS and PPBS were found to be superior over the use of the drugs as individual therapies. This finding advocates the use of a combined pill metformin-teneligliptin therapy for improving patient compliance in diabetes management.

The emergence of gliptins in India, and robust evidence on their overall safety and efficacy have contributed to changing prescribing patterns of anti-diabetic agents in the country. Among the various available combination therapies, metformin-teneligliptin is the second most commonly used for managing T2DM (28.06%). A real-world efficacy assessment based on TREAT-INDIA study has concluded that prescription of teneligliptin,either as monotherapy or as an add-on to one or more commonly used antidiabetic agents, is highly beneficial in improvingglycemic control in Indian subjects.[7] The corresponding HbA1c (%) reductionsin teneligliptin noted when used as monotherapy, add-on to metformin or an-on to metformin plus sulfonylureas combination, add-on to metformin plus alpha–glucosidase inhibitor combination or add-on to insulin were 0.98±0.53, 1.07±0.83, 1.46±1.33, 1.43±0.80, and 1.55±1.05, respectively.[8]

According to the American Diabetic Association, metformin can be used asthe first-line drug for managing T2DM. In patients showing glycemic variability with metformin, the add-on drugs like sulphonylureas, DPP-4 inhibitors or other oral hypoglycemic agents or insulin can be considered.[9] A retrospective study Chudasma et al. has reported that combination of teneligliptin 20mg with metformin 1000 mg is associated with significant reduction in HbA1c.The respective reductions in HbA1c from baseline noted at 12 weeks, 24 weeks and 48 weeks were 1.2%, 1.6% and 1.0%.A comparative study by Nishanth et al. has reported the superiority of metformin (500 mg)-teneligliptin (20 mg) over metformin-glimepiride in improving glycemic and lipid profiles in T2DM patients.[10]

Noncompliance is one of the major factors accountable for the increase in the global prevalence of diabetes. A cross-sectional study conducted among T2DM patients, who attended the diabetic clinic of a medical college in Kolkata, India, has found that the compliance rate of antidiabetic drugs is only 57.7%. The reduced compliance was linked to increasing age, male gender, illiteracy,

poor per capita monthly income, longer duration of diabetes, and type of drug regimens.[11] An observational and a questionnaire-based study carried out by Indu et al. in a tertiary hospital has concluded that the level of polypharmacy is higher in Indian subjects, resulting in increasing the pill burden. The maximum level of polypharmacy (5.82) was noted among geriatric patients between the ages group of 61–70. The study also highlighted the need for more research pertaining to fixed drug combinations to reduce the pill burden, without compromising the safety and efficacy.[12] The present study, though preliminary, holds immense relevance as it corroborates the efficacy of combined pill metformin (500 mg)-teneligliptin (20 mg) in an Indian setting. This combination may serve as effective alternative to metformin/teneligliptin individual therapies, thereby to reduce the pill burden and improve patient compliance.

Single center, lack of randomization and limited samples are the major limitations of the study. Hence, it is not possible to make conclusive evidence-based remarks about the superiority of either of the treatment regimen (teneligliptin/ metformin monotherapy *Vs*. combination therapy). Furthermore, analyzes based on randomized clinical trials are essential to corroborate the study findings and to recommend the appropriate choice of drug for Indian practice setting. Another limitation of the study is not evaluating the effects of other influencing factors such as BMI, lipid profile, hypertension etc.

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