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Original Research Article

Effect of SGLT-2 inhibitor (remogliflozin) plus DPP4 inhibitor (vildagliptin) on diabetic nephropathy in patients with type 2 diabetes mellitus comparison with combination of metformin and sulphonylureas

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ABSTRACT

Background: Diabetes is leading cause of renal failure in entire world. Approximately 20-40 percent of patients with diabetes develop diabetic nephropathy. Newer drugs like SGLT-2 inhibitors and DPP-4 inhibitors are valuable option for Diabetic Nephropathy. Remogliflozin etabonate (RE) is the latest addition to the SGLT2 inhibitor class of drugs that have been recently approved in India for the management of T2DM.This study was conducted to elaborate effect of SGLT2 inhibitor (remogliflozin) plus DPP4 inhibitor (vildagliptin) on diabetic nephropathy in patients of Type 2 DM.

Methods: This hospital based, comparative, open label, randomized controlled trial has been carried out in our department during January 2020 to October 2022 on 60 patients. Group 1 was given metformin 500 mg BD and glimepiride 1 mg BD and group 2 was given FDC of remogliflozin 100 mg and vildagliptin 50 mg BD with 32 patients in group 1 and 28 patients in group 2. The study was approved by ethical committee of our institute.

Results: Mean (SD) of urine ACR in metformin and glimepiride group at screening, 12 weeks, 24 weeks, and at 36 weeks were 93.64 (53.92), 95.56 (52.76), 89.96 (50.22) and 90.9 (53.56) respectively mean (SD) of urine ACR in remogliflozin and vildagliptin group at screening, 12 weeks, 24 weeks, and at 36 weeks were 108.28 (68.5), 100.73 (55.5), 99.35 (55.71) and 75.1 (38.7) respectively. Mean (SD) of eGFR in metformin and glimepiride group at screening, 12 weeks, 24 weeks, and at 36 weeks were 59.62 (18.57), 61.2 (11.1), 60.06 (14.37) and 60.8 (13.3) respectively. Mean (SD) of eGFR in remogliflozin and vildagliptin group at screening, 12 weeks, 24 weeks, and at 36 weeks were 68.03 (16.35), 65.8 (7.96), 66.28 (15.13) and 68.4 (11.6) respectively.

Conclusions: Remogliflozin and vildagliptin combination has significant reduction of proteinuria and eGFR improvement when compared to metformin plus glimepiride.

Keywords: SGLT 2 inhibitors, DPP4 inhibitors, Remogliflozin and vildagliptin, Diabetic nephropathy

INTRODUCTION

According to International Diabetes Federation In 2021, Approximately 537 million adults (20-79 years) are living with diabetes. More than 95% of people with diabetes have type 2 diabetes.[1] India, considered as the 'diabetes capital' of the world, is home to 74 million diabetics with a prevalence of ~8.7% among the adult population.[2] In lower-income groups, the cost of medications may be a reason behind lack of adherence.[3] 20-40 percent of patients with diabetes develop diabetic nephropathy. Diabetic nephropathy is a clinical syndrome in DM patients

characterized by persistent albuminuria (>300 mg/day or >200 µg/min) at 2 out of 3 examinations within 3-6 months, a progressive decrease in GFR, and hypertension. Basically, natural development of DN differs based on the type of diabetes and the presence of albuminuria (30-300 mg/day).

Intervention effective in slowing progression in albuminuria and declining kidney functions include (1) improved glycemic control; (2) strict blood pressure control; (3) ACE inhibitors or ARB; and (4) SGLT2 inhibitors in individual with type 2 diabetes mellitus two recently published clinical trials, the CANVAS trials and EMPA-REG have shown that SGLT2 inhibition not only has cardiovascular benefits but also favourably alters the progression of diabetic nephropathy in patients with T2DM.[4,5] Remogliflozin etabonate (RE) is the latest addition to the SGLT2 inhibitor class of drugs that have been recently approved in India for the management of T2DM.[6]

A recent study revealed that remogliflozin significantly reduced albuminuria (p value<0.001) in type 2 diabetes mellitus patients with delay in progression of diabetic nephropathy as compared to placebo.[7] Dipeptidyl peptidase-4 (DPP-4) inhibitors are another group of medications used for glycaemic control and treatment of DN in patients with type 2 DM.

DDP-4 enzymes are suggested to have roles in the progression of kidney injury in patients with DN considering their inflammatory functions. Therefore, inhibiting DDP-4 function is one of the therapeutic targets in patients with DN; however, there are controversies regarding the effects of DDP-4 inhibitors on kidney injury in these patients.[8] Vildagliptin may be used in the standard dosage (50 mg twice daily) in patients with mild renal impairment (CrCl≥50 ml/min), whereas one-half of the usual dose (50 mg once daily) is recommended in patients with moderate-to severe renal insufficiency (CrCl<50 ml/min) and those with ESRD.[9] So, we have conducted this study to elaborate effect of SGLT2 inhibitor (remogliflozin) plus DPP4 inhibitor (vildagliptin) on diabetic nephropathy in patients of type 2 DM.

METHODS

This hospital based, comparative, open label, randomized controlled trial has been carried out in department of medicine of our institute of North India during January 2020 to October 2022 on 60 patients.

Group 1 was given metformin 500 mg BD and glimepiride 1 mg BD and group 2 was given fixed dose combination of remogliflozin 100 mg and vildagliptin 50 mg BD with 32 patients in group 1 and 28 patients in group 2.

The study was approved by ethical committee of institute and all participants provided written informed consent before the data collection.

Inclusion criteria

Patients with following were included- (a) age>18 years; (b) either sex (M/F); and (c) type 2 DM with HbA1C between 6.5% to 10%.

Exclusion criteria

Patients with (a) HbA1C > 10.0; (b) patients with age <18 years or >65; (b) with type 1 diabetes mellitus; (c) with CKD due to other cause (ADPKD, glomerulonephritis); (d) who were terminally ill; (e) on haemodialysis; (f) pregnancy; and (g) GFR<45 ml/min/1.73 m^2.

Methodology

Total 70 patients with type II diabetes mellitus were enrolled for study and divided into two groups- (a) group 1- patients were given metformin 500 mg BID and glimepiride 1 mg BID; (b) group 2- patients were given FDC of remogliflozin 100 mg and vildagliptin 50 mg BID. 3 patients in metformin+glimepiride group and 7 patients in remogliflozin+vildagliptin group were lost to follow up. eGFR (ml/min/1.73 m^2) was calculated using CKD- EPI equation. Urine ACR (mg/g) was measured using Nephelometry method. Patients were followed up at 12 weeks, 24 weeks, and 36 weeks with measurement of Urine ACR, serum creatinine.

RESULTS

32 patients in group 1 (metformin plus glimepiride group) and 28 patients in group 2 (remogliflozin plus vildagliptin) were analysed. We found that mean (SD) of age (in years) of participants in metformin and glimepiride group is 51.81 (6.48) and remogliflozin and vildagliptin group is 50 (8.21) (Table 1 and Figure 1).

We found that mean (SD) of urine ACR in metformin and glimepiride group at screening, 12 weeks, 24 weeks, and at 36 weeks were 93.64 (53.92), 95.56 (52.76), 89.96 (50.22) and 90.9 (53.56) respectively (Table 2). Mean (SD) of urine ACR in remogliflozin and vildagliptin group at screening, 12 weeks, 24 weeks, and at 36 weeks were 108.28 (68.5), 100.73 (55.5), 99.35 (55.71) and 75.1 (38.7) respectively (Figure 2).

Mean (SD) of eGFR in metformin and glimepiride group at screening, 12 weeks, 24 weeks, and at 36 weeks were 59.62 (18.57), 61.2 (11.1), 60.06 (14.37) and 60.8 (13.3) respectively (Table 3). Mean (SD) of eGFR in remogliflozin and vildagliptin group at screening, 12 weeks, 24 weeks, and at 36 weeks were 68.03 (16.35), 65.8 (7.96), 66.28 (15.13) and 68.4 (11.6) respectively (Figure 3).

Mean (SD) of serum creatinine in metformin and glimepiride group at screening, 12 weeks, 24 weeks, and at 36 weeks were 1.34 (0.26), 1.26 (0.164), 1.28 (0.2) and 1.27 (0.15) respectively (Table 4). Mean (SD) of

creatinine in remogliflozin and vildagliptin group at screening, 12 weeks, 24 weeks, and at 36 weeks were 1.22 (0.24), 1.22 (0.129), 1.23 (0.18) and 1.10 (0.10) respectively (Figure 4).

Table 1: Comparison of mean age between the two groups (N=60).

Age of the patient in years	Group 1 metformin+glimepiride (N=32)	Group 2 remogliflozin+vildagliptin (n=28)	P value
	51.81 (6.48)	50 (8.21)	0.344

Table 2: Mean ACR in 2 groups.

Mean ACR	Group 1 metformin+glimepiride (n=32)	Group 2 remogliflozin+vildagliptin (n=28)	P value
Screening	93.64 (53.92)	108.28 (68.5)	0.359
12 weeks	95.56 (52.76)	100.73 (55.5)	0.713
24 weeks	89.96 (50.22)	99.35 (55.71)	0.495
36 weeks	90.9 (53.56)	75.1 (38.7)	0.201
P value (intragroup)	0.090	<0.001	

Table 3: Mean (SD) of eGFR.

Mean (SD)	Group 1 metformin+glimepiride (n=32)	Group 2 remogliflozin+vildagliptin (n=28)	P value
Screening	59.62 (18.57)	68.03 (16.35)	0.070
12 weeks	61.2 (11.1)	65.8. (7.96)	0.070
24 weeks	60.06 (14.37)	66.28 (15.13)	0.108
36 weeks	60.8 (13.3)	74.4 (9.93)	0.001
P value (intragroup)	0.70	0.04	

Table 4: Mean (SD) of serum creatinine.

Mean (SD)	Group 1 metformin+glimepiride (n=32)	Group 2 remogliflozin+vildagliptin (n=28)	P value
Screening	1.34 (0.26)	1.22 (0.24)	0.084
12 weeks	1.26 (0.164)	1.22 (0.129)	0.364
24 weeks	1.28 (0.2)	1.23 (0.18)	0.332
36 weeks	1.27 (0.15)	1.10 (0.10)	0.001
P value (intragroup)	0.142	0.006	

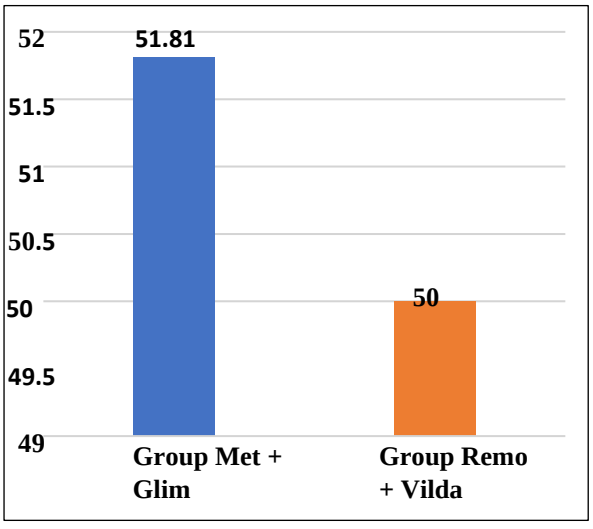

Figure 1: Distribution of cases according to age (years) in the two groups.

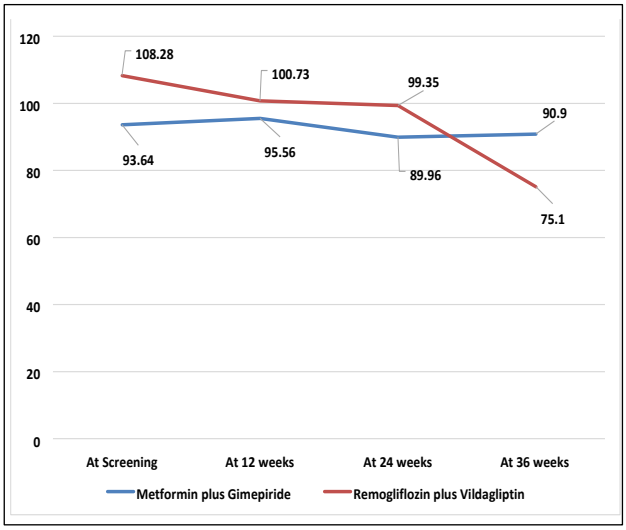

Figure 2: Mean ACR in 2 groups.

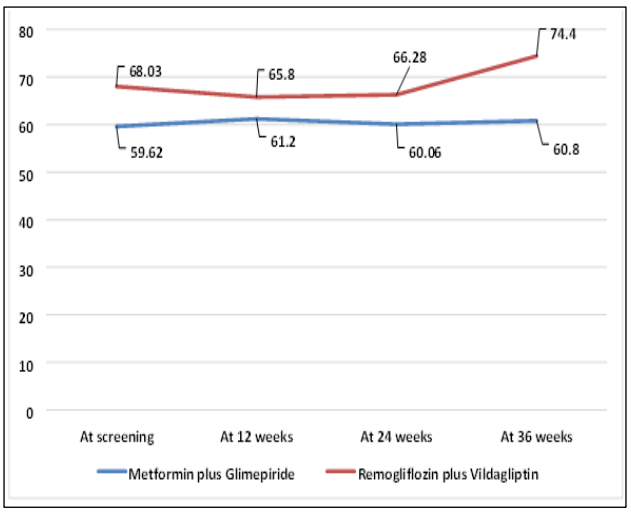

Figure 3: Mean (SD) of eGFR.

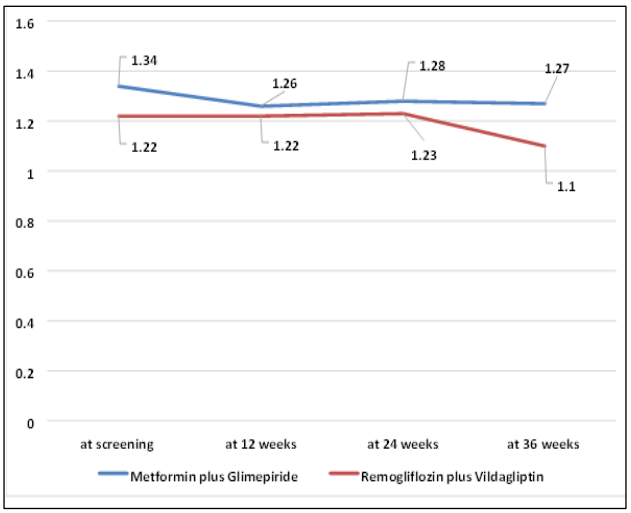

Figure 4: Mean (SD) of serum creatinine.

DISCUSSION

Diabetic nephropathy (DN) is the leading cause of end-stage renal disease world-wide. There are various drugs available for treatment of diabetic nephropathy. Newer drugs like SGLT-2 inhibitors and DPP-4 inhibitors are valuable option. Few studies have been done to see effect of combination of SGLT-2 inhibitors and DPP-4 inhibitors on diabetic nephropathy/delay progression of diabetic nephropathy. Results of our study showed significant change in proteinuria, eGFR in remogliflozin and vildagliptin group in compare to metformin and SU group.

In our study we found that mean (SD) of urine ACR in metformin and glimepiride group at screening, 12 weeks, 24 weeks, and at 36 weeks were 93.64 (53.92) ,95.56 (52.76), 89.96 (50.22) and 90.9 (53.56) respectively with p value 0.09 at 36 weeks which was significant. Mean of urine ACR in remogliflozin and vildagliptin group at screening, 12 weeks, 24 weeks, and at 36 weeks were 108.28, 100.73, 99.35 and 75.1 respectively (p value<0.001 at 36 weeks). There was significant reduction in urine ACR in remogliflozin plus vildagliptin group at 36 weeks while there was not significant reduction in urine ACR in metformin plus glimepiride group.

Leiter et al observed in a randomized, double-blind study, patients (n=1,450) who received canagliflozin 100 or 300 mg, or glimepiride (titrated up to 6 or 8 mg/day) over period of 1 week that the pattern of change in eGFR was different between the canagliflozin groups and the glimepiride group, with decreases in eGFR that occurred early after initiation of therapy and subsequently attenuated and remained stable over 104 weeks seen with treatment with both canagliflozin doses, versus a progressive decline in eGFR throughout the 104-week treatment period observed with treatment with glimepiride.[10]

Neal et al studied in CANVAS trial that progression of albuminuria occurred less frequently among participants assigned to canagliflozin than among those assigned to placebo (89.4 verses 128.7 participants with an event per 1000 patient with an event per 1000 patient- years) corresponding to 44a hazard ratio of 0.73 (95% CI, 0.67 to 0.79) (Figure 3 and 5); the effects were greater in CANVAS-R (hazard ratio, 0.64; 95% CI, 0.57 to 0.73) than in CANVAS (hazard ratio, 0.80; 95% CI, 0.72 to 0.90) (p=0.02 for homogeneity).[11] Regression of albuminuria also occurred more frequently among those assigned to canagliflozin than among those assigned to placebo (293.4 verses 187.5 participants with regression per 1000 patient-years; hazard ratio, 1.70; 95% CI, 1.51 to 1.91). Rosenstock et al studied in CARMELINA clinical trial that progression of albuminuria category i. e.; change from normo- albuminuria microalbuminuria macroalbuminuria or change from microalbuminuria to macroalbuminuria) occurred less frequently in the linagliptin group [763/2162 (35.3%); 21.4 per 100 person-years] than in the placebo group [819/2129 (38.5%)]; 24.5 per 100 person-years; absolute incidence rate difference, -3.18; 95% CI, -5.44 to -0.92) (HR, 0.86; 95% CI, 0.78-0.95; p=0.003). Gharabaghi et al observed in a randomized, double-blind, parallel trial that the decrease in albuminuria was greater in the empaglifozin group compared to the linagliptin group (p=0.001, Cohen's d=0.98).[12,13] After adjusting for baseline values of albuminuria and HbA1C, changes in the albuminuria were significantly different between groups in favor of the empaglifozin group (p value<0.001).

Nag et al observed in clinical observational study of 103 patients to evaluate the therapeutic efficacy of vildagliptin on microalbuminuria in type 2 diabetes mellitus that the mean of ACR baseline (mean±SD) of patients was 125.2436±58.810 with range 50.70- 298.00 and the median was 100.0000.[14] The mean of ACR 3 months (mean±SD) of patients was 110.3184±57.5647 with range 38.70-265.00 and the median was 86.0000. The mean of ACR 6 months (mean±SD) of patients was 106.7340±48.8492 with range 37.0000-231.0000 and the median was 92.0000. The mean of ACR 9 months

(mean±SD) of patients was 103.7252±45.6745 with range 21.5000-209.0000 and the median was 102.0000. The mean of ACR 12 months (mean±SD) of patients was 95.4460±62.342 with range 1,00,000-26,00,000 and the median was 7,00,000. Association of ACR in five groups was not statistically significant (p=0.6118).

In our study we found that Mean (SD) of eGFR in metformin and glimepiride group at screening, 12 weeks, 24 weeks, and at 36 weeks were 59.62 (18.57), 61.2 (11.1), 60.06 (14.37) and 60.8 (13.3) respectively with p value 0.323 at 36 weeks which was non- significant. Mean (SD) of eGFR in remogliflozin and vildagliptin group at screening, 12 weeks, 24 weeks, and at 36 weeks were 68.03 (16.35), 65.8(7.96), 66.28 (15.13) and 74.4 (9.93) respectively with p value 0.04 at 36 weeks which was non-significant. Inter group p value for eGFR at 36 weeks was 0.001 which showed significant improvement in eGFR in remogliflozin plus vildagliptin group compared to metformin plus vildagliptin group. Gharabaghi et al observed in randomized Mohammad, double-blind, parallel trial over 12 weeks period e GFR, values were significantly improved in patients who received empaglifozin (p<0.001).[13]

In the Linagliptin group, GFR was significantly decreased after the intervention (p<0.001) inter group comparison p value was >0.05. In our study Mean (SD) of eGFR in metformin and glimepiride group at screening, 12 weeks, 24 weeks, and at 36 weeks were 59.62 (18.57), 61.2 (11.1), 60.06 (14.37) and 60.8 (13.3) respectively with p value 0.323 at 36 weeks which was non- significant. Mean (SD) of eGFR in remogliflozin and vildagliptin group at screening, 12 weeks, 24 weeks, and at 36 weeks were 68.03 (16.35), 65.8(7.96), 66.28 (15.13) and 74.4 (9.93) respectively with p value 0.04 at 36 weeks which was non-significant. Inter group p value for eGFR at 36 weeks was 0.001 which showed significant improvement in eGFR in remogliflozin plus vildagliptin group compared to metformin plus vildagliptin group. Heerspink et al studied in DAPA CKD trial that least-squares mean±SE estimated GFR slopes from baseline to 30 months in the dapagliflozin and placebo groups were -2.86±0.11 and -3.79±0.11 ml per minute per 1.73 m^2 per year, respectively, resulting in a between-group difference of 0.93 ml per minute per 1.73 m^2 per year (95% CI, 0.61 to 1.25).[15]

During the first 2 weeks, there was a greater reduction in the estimated GFR in the dapagliflozin group than in the placebo group (-3.97±0.15 verses 0.82±0.15 ml per minute per 1.73 m^2). Thereafter, the annual change in the mean estimated GFR was smaller with dapagliflozin than with placebo (-1.67±0.11 and -3.59±0.11 ml per minute per 1.73 m^2, respectively), for a between-group difference of 1.92 ml per minute per 1.73 m^2 per year (95% CI, 1.61 to 2.24). Treatment-naive patients with T2DM for whom metformin is contraindicated or who are metformin intolerant and HbA1c is >8% and in patients uncontrolled on metformin with HbA1c of 8.5% can be initiated a combination therapy with a SGLT2i an DPP4i FDC along with lifestyle modification.[16] Although number of cases in our study was small but this study revealed that combination of SGLT 2 inhibitor and DPP4 inhibitor can be better choice for patients of diabetic nephropathy.

CONCLUSION

There was significant reduction in urine ACR in remogliflozin plus vildagliptin group at 36 weeks while there was no significant reduction in urine ACR in metformin plus glimepiride group so combination of remogliflozin plus vildagliptin is better than metformin plus SU. Hence combination SGLT 2 inhibitor and DPP4 inhibitor may delay the progression of diabetic nephropathy and may improve eGFR in patients of diabetic nephropathy.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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