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Diabetic Kidney Disease Can Be Reversed with a Combination of SGLT- 2 and DPP- 4 Inhibitors in Patients of Type - II Diabetes Mellitus with Kidney Injury

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ABSTRACT

Background

Diabetic kidney disease (DKD) is a frequent and serious complication of type II diabetes mellitus (T2DM), and represents end organ damage due to advanced glycation end-products (AGE). Glycemic control is important to reduce kidney injury due to AGE. We conducted a pilot study to compare the outcomes on kidney function, with two sets of oral hypoglycemic agents (OHA) used for treating T2DM. Remogliflozin Etabonate and Vildagliptin are twice-daily medications that are individually approved and widely used in India for the treatment of diabetes. A fixed dose combination of remogliflozin and vildagliptin is available, offering better glycemic control and compliance, by reducing the pill burden and offering a simplified treatment regimen.

Materials and methods

T2DM patients were randomized into groups 1 and 2, after applying exclusion criteria. Group 1, with 32 patients, received a fixed dose combination (FDC) of biguanide and sulfonyurea, namely metformin 500 mg plus glimepiride 1 mg, twice daily. Group 2, with 28 patients, received a FDC of SGLT-2 inhibitor and DPP-4 inhibitor, remogliflozin 100 mg plus vildagliptin 50 mg, twice daily. Physical and metabolic parameters were assessed at the beginning of the study and later at 12, 24 and 36 weeks after initiation of therapy. Statistical analysis was done

using unpaired t-test to compare the difference between the two groups.

Result

In group 1, serum creatinine levels reduced from 1.34 ± 0.26 at baseline to 1.27 ± 0.15 after 36 weeks, while in group 2 they reduced from 1.22 ± 0.24 to 1.1 ± 0.1 after the same time period ($p<0.05$ between the two groups). The eGFR increased in group 1 from 60 ± 19 at baseline to 61 ± 13 after 36 weeks, while the corresponding improvement in group 2 was 68 ± 16 to 74 ± 10 ($p<0.05$). Other parameters including change in body weight, fasting blood glucose (FBG), post prandial blood glucose (PPBG), glycosylated hemoglobin (HbA1c) and albumin-creatinine ratio (ACR), did not show a significant difference between the two groups.

Conclusion

A combination of SGLT-2 inhibitor and DPP-4 inhibitor to treat T2DM, significantly improves kidney function in patients with DKD after 36 weeks of treatment, compared to conventional therapy with a combination of biguanide and sulfonylurea, as evidenced by a significant decrease in serum creatinine and improvement in eGFR.

Keywords

Diabetic kidney disease, Remogliflozin Etabonate, Vildagliptin.

INTRODUCTION

Diabetic kidney disease (DKD) is a long-term complication of (T2DM), and the leading cause of chronic kidney disease (CKD)[1,2,3]. It is associated with other complications like hypertension, dyslipidaemia and a higher cardiovascular risk. Conventional prevention and management protocols often slow the decline in kidney function, but newer agents may even improve function of already affected kidneys[13,14,15,16].

This study compares the renal outcomes of managing T2DM using a combination of conventional oral hypoglycaemic agents (OHA) sulfonylurea and biguanides, with newer ones including SGLT-2 inhibitors and DPP-4 inhibitors.

Materials and Methods

This was a prospective cohort observational study between January 2022 and December 2022. Patients above 18 years of age diagnosed with T2DM [by the International Classification of Diseases, Tenth Revision (ICD-10), or haemoglobin A1c (HbA1c) ≥6.5%], were studied in LLR Hospital, Kanpur, in the renal clinic. Ethics approval was obtained from the Institutional Review Board (IRB)

Inclusion Criteria

for referral of DKD patients to the renal clinic were according to the Kidney Disease: Improving Global Outcomes (KDIGO) 2012 clinical practice guidelines for the evaluation of CKD. Patients of diabetes mellitus (T2DM) with:

1. Increasing urine albumin/creatinine ratio (ACR)
2. Albuminuria:

- Persistent macro-albuminuria >300 with preserved eGFR (≥60 mL/min)
- uACR >300 mg/mmol on two separate occasions and stage 3-4 CKD (eGFR 15–59 mL/min/1.73 m^2)

Exclusion Criteria

for referral to the DKD clinic were:

1. Comorbidities that preclude renal retardation, such as terminal cancers
2. Limited life expectancy due to advanced organ failure

3. Cognitive impairment or psychiatric illness
4. Patients with stage 5 CKD or on dialysis were excluded.

The treatment groups were randomised to two groups: Group 1 received a fixed dose combination of glimepiride 1 mg plus metformin 500 mg administered twice daily. Group 2 patients received a fixed dose combination of remogliflozin 100 mg plus vildagliptin 50 mg, twice daily. These were in addition to other medication including antihypertensives, lipid lowering therapy and dietary supplements where indicated.

Blood samples for fasting and post prandial plasma glucose (FPG and PPPG), serum creatinine (S.cr.) and HbA1c, and spot urine for albumin (and calculating albumin-creatinine ratio (ACR)), were collected and measured at the hospital laboratory. The Chronic Kidney Disease Epidemiology Collaboration equation was used to estimate eGFR.

STATISTICAL ANALYSIS

Continuous variables were expressed as mean ± standard deviation (SD) and the difference in mean test with unequal variance (unpaired t-test) with conservative degrees of freedom (=27) at a 5 percent significance level, were used for comparing values between the two groups for various parameters, at baseline, 12, 24 and 36 weeks. The results were considered statistically significant for $P < .05$.

RESULTS

The duration of follow-up was up to 1 year (median 9 months). There were 60 patients after randomisation, 32 in group 1 and 28 patients in group 2. Their respective demographic details are given in table 1 below:

Table 1: Comparison of Groups 1 and 2 with diabetes mellitus

Criteria	Group 1	Group 2
Number of patients	32	28
Age (years)	51.81	50
±SD	6.48	8.21
Male	16	18
Female	16	10

Both groups had similar numbers of patients with similar age groups and genders.

Table 2: The different parameters recorded during the course of the study are shown in below:

Body Weight	Control	12 weeks	24 weeks	36 weeks
Group 1	67.37	67.4	67.63	67.67
±SD	8.61	8.59	8.63	8.63
Group 2	66.37	66.33	66.18	65.65
±SD	7.3	7.25	7.13	6.88

P value	NS	NS	NS	NS
Serum creatinine	**Control**	**12 weeks**	**24 weeks**	**36 weeks**
Group 1	1.34	1.26	1.28	1.27
±SD	0.26	0.164	0.2	0.15
Group 2	1.22	1.22	1.23	1.1
±SD	0.24	0.129	0.18	0.1
P value	NS	NS	NS	**p<0.05**
eGFR	**Control**	**12 weeks**	**24 weeks**	**36 weeks**
Group 1	59.62	61.2	60.06	60.8
±SD	18.57	11.1	14.37	13.3
Group 2	68.03	65.8	66.28	74.4
±SD	16.35	7.96	15.13	9.93
P value	NS	NS	NS	**p<0.05**
Glycosylated haemoglobin (HbA1c)	**Control**	**12 weeks**	**24 weeks**	**36 weeks**
Group 1	8.22	8.05	8.01	7.67
±SD	1.21	1.14	1.12	1.62
Group 2	7.88	7.79	7.73	7.7
±SD	0.96	0.9	0.9	0.89
P value	NS	NS	NS	NS
Fasting Blood Sugar	**Control**	**12 weeks**	**24 weeks**	**36 weeks**
Group 1	137.37	115.71	117.62	117.03
±SD	19.86	11.43	8.76	7.71
Group 2	127.03	109.32	118.57	113.6
±SD	12.87	9.62	9.46	9.28
P value	NS	NS	NS	NS
Post Prandial Blood Sugar	**Control**	**12 weeks**	**24 weeks**	**36 weeks**
Group 1	235.31	181.4	188.03	192.5
±SD	54.14	16.61	13.34	12.22

Group 2	215	177.6	196.75	190.21
±SD	18	9.57	14.02	11.04
P value	NS	NS	NS	NS
Urine ACR	**Control**	**12 weeks**	**24 weeks**	**36 weeks**
Group 1	93.64	95.56	89.96	90.9
±SD	53.92	52.76	50.22	53.56
Group 2	108.28	100.73	99.35	75.1
±SD	68.5	55.5	55.71	38.7
P value	NS	NS	NS	NS

There was a significant improvement in kidney function in group 2 patients after 36 weeks of treatment with the combination of SGLT2 inhibitor and DPP4 inhibitors. This is seen as a significant reduction in the serum creatinine and increase in eGFR ($p<0.05$). Urine ACR was not significantly affected, though a trend towards improvement was seen, when compared to the baseline reading. Other parameters like body weight, HbA1c, fasting and post prandial blood glucose levels were similar in both groups, with no statistically significant (p=NS) change from baseline after 36 weeks of treatment.

DISCUSSION

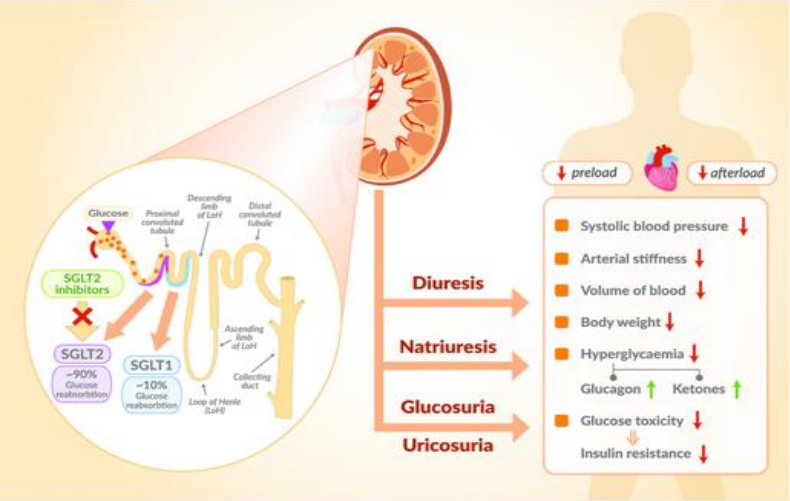
An increasing prevalence of diabetic kidney disease (DKD) progressing to end-stage kidney disease (ESKD) is observed, with half of the patients with type 2 diabetes mellitus (T2DM)[1,2,3] suffering from chronic kidney disease (CKD), and two thirds of ESKD patients having pre-existing DKD[4,5]. This study highlights the clinical benefit of using the sodium–glucose cotransporter 2 inhibitor (SGLT2i)[15,16], remogliflozin, in combination with dipeptidyl peptidase inhibitor (DPP4i)[13,14,] vildagliptin, to improve renal outcomes in DKD.

Mechanism of action:

Hyperglycemia and DKD: Multiple effects like, metabolic disturbances, glomerular blood flow changes, and inflammatory factors contribute to kidney damage in DKD[7]. These may cause glomerular hyper filtration and glomerular hypertrophy, which may lead to scleros. Arteriolar hyalinosis, tubulointerstitial inflammation, and fibrosis cause increasing permeability to albumin, marked by albuminuria, resulting from progressive glomerular injury. Albuminuria also worsens glomerular hyper filtration. Albuminuria typically develops prior to loss of filtration, but eGFR decline may also occur without the occurrence of albuminuria in DKD. In people who experience a decline in eGFR without albuminuria, the kidney tissue typically shows prominent vascular lesions and interstitial fibrosis[8,9,10].

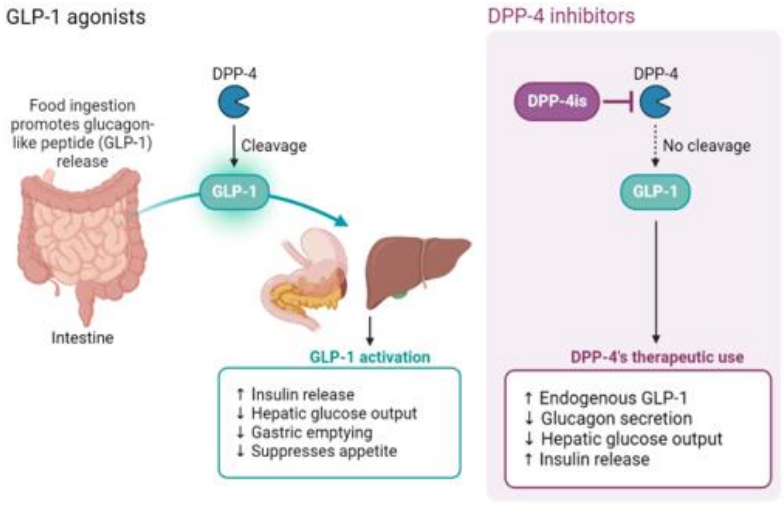
Sodium Glucose Cotransporter 2 Inhibitors: SGLT2i reduces intra glomerular pressure, reducing albumin excretion. Its glycosuric, anti-hyperglycaemic and antihypertensive effects are seen to provide renal protection in cardiovascular outcome trials too. The benefits of SGLT2 inhibition are best seen in DKD patients with a eGFR $\geq$ 45 mL/min/1.73 m^2. However,

its haemodynamic, anti-proteinuric and anti-metabolic effects may be seen despite reducing eGFR[15,16].



The pleiotropic effects of SGLT2i (anti-inflammatory, anti-oxidative and anti-fibrotic) on the heart and liver, in addition to the kidneys, benefit patients of more advanced CKD. Renal outcome trials such as the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) and the Study of Heart and Kidney Protection with Empagliflozin (EMPA-KIDNEY) included patients with an eGFR of 25 and 20 mL/min/1.73 m^2, respectively, proving that the renoprotective effects of SGLT2is can be extended to patients with advanced CKD[7,15,16].

Dipeptidyl peptidase-4 (DPP-4) inhibitors are a glucose-lowering treatment for type 2 diabetes. They work by inhibiting the degradation of incretin hormones, such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP). This increases the concentration of these hormones in the body, which can lead to improved insulin secretion and reduced glucagon secretion. These effects can help to increase glucose utilization, reduce hepatic glucose production, and lower blood sugar levels.



CONCLUSION

Optimal management of blood glucose is the first step in preventing the onset of DKD. Both sodium glucose transport protein 2 inhibitors (SGLT2i) and glucagon like peptide-1 receptor agonists (GLP-1 RA) have shown beneficial effects on DKD, such as a reduction in albuminuria or lower risk of new-onset albuminuria, largely beyond glycemic control. Large scale studies are needed to amplify on other benefits of these newer OHAs in patients with DKD and prevention of diabetic complication. Conventional agents like sulfonylureas and biguanides may offer familiarity and glycemic control. However, the benefits of reversing renal complication with newer agents is worthy of consideration as first line of treatment to provide optimal benefits.

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