Original Article

Comparing The Effect Of The SGLT-2 Inhibitors And DPP-4 Inhibitor Combined Therapy With Sulphonylureas And Metformin Combined Therapy In Patients With Type 2 Diabetic Nephropathy

Sajid Ali[1], Muhammad Ghazi Asad Khan[2], Tazeem Hussain[3], Shahid Latif[4], Bismah Memon[5], Amanullah Lail[6]

1. Sajid Ali, General Practitioner, Primary & Secondary Healthcare Department, MOH, Kuwait. email: drsajid.ali86@gmail.com (Corresponding author)
2. Muhammad Ghazi Asad Khan, Graduate, Liaquat University of Medical and Health Sciences Jamshoro Pakistan. email: ghaziasad9001@gmail.com
3. Tazeem Hussain, Consultant Medicine, FM Academy & Department, King Saud Medical City Riyadh. KSA. email: tzmhussain@yahoo.com
4. Shahid Latif, General Practitioner, Primary & Secondary Healthcare Department, MOH, Kuwait. email: drshahid.1982@gmail.com
5. Bismah Memon, Graduate, Isra University Hyderabad Pakistan. email: bismahmemon12@gmail.com
6. Amanullah Lail, Assistant Professor pediatrics, DMC/DUHS Civil Hospital Karachi Pakistan. email: aman_lail@yahoo.com

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Abstract

Background: Diabetic Mellitus is a leading etiology of renal failure globally. About 20% to 40% of patients with diabetes tend to develop diabetic nephropathy. DPP-4 inhibitors and SGLT-2 inhibitors are quite helpful medications for Diabetic Nephropathy. Remogliflozin etabonate (RE) is a recent addition to the SGLT-2 inhibitor group for the management of type 2 diabetes mellitus (T2DM).

Objective: The present study was conducted to describe the effects of the combination of SGLT-2 inhibitors and DPP-4 inhibitors in comparison to the combination of sulphonylureas and metformin on patients with diabetic nephropathy in T2DM.

Study design: a randomized controlled trial

Place and Duration: This study was conducted in the Primary and Secondary Healthcare Department, MOH, Kuwait, from January 2022 to January 2023.

Methodology: The study includes a total of 104 patients with type 2 DM and diabetic nephropathy. The patients have been divided into two groups, i.e., Group A and Group B. Group A was given glimepiride 1 mg twice daily and metformin 500 mg twice daily. Group B was given SGLT-2 inhibitors (remogliflizone 100mg) twice daily and DPP-4 inhibitors (vildagliptin 50 mg) twice daily. A total of 52 patients were allotted to group A, and 52 patients were allotted to group B. The urine ACR, creatinine, and eGFR of all the patients were measured at the time of screening, the 12th week, the 24th week, and the 36th week of initiation of treatment.

Results: The mean ACR of urine in the patients in Group A was 93.54 at the time of screening before starting the treatment, 95.78 at the 12th week, 89.85 at the 24th week, and 90.8 at the 36th week of treatment. The mean ACR of urine in the patients in Group B was 108.17 at the time of screening, 100.42 at the 12th week, 99.68 at the 24th week, and 75.02 at the 36th week of treatment. The

mean eGFR in Group A at screening was 59.51; it was 61.3 in the 12th week, 60.3 in the 24th, and 60.7 in the 36th week. The mean eGFR in Group B at the screening was 68.02; it was 65.7 in the 12th week, 66.17 in the 24th, and 68.1 in the 36th week.

Conclusion: The vidagliptin and Remogliflozin combination is helpful in a significant reduction in proteinuria and has shown improvement in eGFR compared to the combination of glimepiride and metformin.

Keywords: Remogliflozin, SGLT-2 inhibitors, Vildagliptin, DPP4 inhibitors, Diabetic nephropathy.

Introduction

According to the International Diabetes Federation, about 537 million people aged 20 to 79 will have been diagnosed with diabetes in 2021. Out of all these patients, 95% were suffering from T2DM [1]. The disease is more commonly seen in third-world countries. The most probable reason for these statistics is that drugs are not affordable for most of the masses [2]. Another cause of this prevalence is a lack of education, which leads to a lack of compliance with the medication [3]. Almost half of the patients tend to develop complications from DM. Overall, 20–40% of patients have shown the development of diabetic nephropathy [4]. The disease is characterized by proteinuria at two out of three examinations within six months, hypertension, and a progressive decline in the eGFR. The natural course of diabetic nephropathy depends on the type of DM and the level of proteinuria [5].

A few regimens that help in the effectiveness of the intervention in slowing the deterioration of the functions of the kidneys and decreasing the progression of proteinuria are improvement of glycemic control, strict maintenance of blood pressure, ARB or ACE inhibitors, and SGLT-2 inhibitors in patients with T2DM. These interventions have cardiovascular benefits and also protect the kidneys from diabetic nephropathy in diabetic patients [6].

Remogliflozin reduced proteinuria significantly in patients with T2DM and diabetic nephropathy. DPP-4 inhibitors are also used for effective glycemic control and diabetic nephropathy management [7]. The efficacy of this drug is obvious because of the renal tissue damage caused by DPP-4 enzymes. These enzymes perform their function as inflammatory factors [8].

The present study compared the combined effect of DPP-4 inhibitors and SGLT-2 inhibitors with the combination therapy of metformin and sulfonylureas in the treatment of diabetic nephropathy in patients with T2DM.

Methodology

The present study is a randomized controlled trial. There were a total of 104 patients in the present study. The patients were divided into two groups: Group A and Group B. Each group had 52 patients. The patients in Group A were administered metformin 500 mg twice daily and glimepiride 1 mg twice daily. The patients in Group B were given linagliptin 50 mg twice daily and remogliflozin 100 mg twice daily. The calculation of eGFR was done using the CKD-EPI equation. The nephelometry method was used for the measurement of Urine ACR. The patients were asked to attend on the 12th, 24th, and 36th weeks. At each visit, the Urine ACR and serum creatinine of the patients were measured.

All the patients and their attendants were informed about the purpose and methodology of the research and were asked for written consent.

According to the inclusion criteria of the study, only patients over the age of 18 with type 2 DM and HBA1C 6.5–10% were added to the present study. The patients added to the study were of both genders. As per the exclusion criteria of the present study, patients having HBA1C of more than 10%, age more than 65 years, having type 1 DM,

already presenting with CKD, terminally ill, on dialysis, pregnant patients, and patients having a GFR less than 45 were excluded from the study.

Results

A total of 52 patients were present in Group A of the study (taking metformin and glimepiride), and 52 patients were present in Group B (taking vildagliptin and Remogliflozin). The mean age of the patients in Group A was 51.76 ± 6.76 years and 50.64 ± 8.68 years in Group B.

It was found that the mean ACR of urine in the patients in Group A was 93.54 at the time of screening before starting the treatment, 95.78 at the 12th week, 89.85 at the 24th week, and 90.8 at the 36th week of treatment. The mean ACR of urine in the patients in Group B was 108.17 at the time of screening, 100.42 at the 12th week, 99.68 at the 24th week, and 75.02 at the 36th week of treatment. The data is given in Table 1.

Table 1. Mean ACR in both the groups

Time of investigation	Mean ACR		p-value
	Group A (n=52)	Group B (n=52)	
Screening	93.54	108.17	0.315
12th week	95.78	100.42	0.746
24th week	89.85	99.68	0.421
36th week	90.8	75.02	0.224
Intra-group P-value	0.091	<0.001	

The mean eGFR in Group A at screening was 59.51; it was 61.3 in the 12th week, 60.3 in the 24th, and 60.7 in the 36th week. The mean eGFR in Group B at the screening was 68.02; it was 65.7 in the 12th week, 66.17 in the 24th, and 68.1 in the 36th week. The data has been shown in Table 2.

Table 2. Mean eGFR in both the groups

Time of investigation	Mean eGFR		p-value
	Group A (n=52)	Group B (n=52)	
Screening	53.51	68.02	0.071
12th week	61.3	65.7	0.071
24th week	60.3	66.17	0.148
36th week	60.7	68.1	0.001
Intra-group P-value	0.710	0.042	

The mean creatinine in Group A at the screening was 1.35; it was 1.27 in the 12th week, 1.29 in the 24th, and 1.28 in the 36th week. The mean creatinine in Group B at the screening was 1.23; it was 1.23 in the 12th week, 1.24 in the 24th, and 1.11 in the 36th week. The data has been tabulated in Table 3.

Table 3. Mean creatinine in both the groups

Time of investigation	Mean creatinine		p-value
	Group A (n=52)	Group B (n=52)	
Screening	1.35	1.23	0.085
12th week	1.27	1.23	0.397

24th week	1.29	1.24	0.365
36th week	1.28	1.11	0.001
Intra-group P-value	0.175	0.006	

Discussion

Diabetic nephropathy is one of the leading causes of kidney failure globally. There are many treatment options for diabetic nephropathy. For a patient with T2DM, DPP-4 inhibitors and SGLT-2 inhibitors are considered effective options. However, there are not many studies done on the combined effects of these two drug groups. The present study has compared the combined effect of DPP-4 inhibitors and SGLT-2 inhibitors with the combination therapy of metformin and glimepiride. It has been seen in the current study that the combination of DPP-4 inhibitors and SGLT-2 inhibitors is significantly effective in controlling proteinuria, urine ACR, and eGFR in diabetic retinopathy patients.

Jamal et al. conducted a study to assess the progress of the treatment and its prospects. They described that the treatment of diabetic nephropathy has various challenges, and regular investigations must be carried out to evaluate the efficacy of new treatments [9]. The present study investigated the patients at the time of screening, the 12th week, the 24th week, and the 36th week after the treatment was initiated. Noel et al. carried out their study to find out the updated management of diabetic nephropathy. According to their study, renin-angiotensin-aldosterone system blockade is the key to keeping the kidneys safe in patients with diabetic nephropathy. They have suggested combination therapy for the management of diabetic nephropathy [10].

According to the study of Zou et al., SGLT-2 inhibitors, along with DPP-4 inhibitors, mineralocorticoid blockers, and angiotensin receptor blockers, have shown potential benefits in the management of diabetic nephropathy. However, they suggested research on larger randomized controlled trials for the investigation of the effects of this combination therapy. The cardiovascular safety of these drugs also needs to be checked in patients with diabetic nephropathy [11].

Birnbaum et al. conducted a study to see the combined effect of SGLT-2 and DPP-4 inhibitors on mice with T2DM. Contrary to the present study, they did not notice any significant effect of the drugs on the management of diabetic nephropathy in those mice. They suggested further clinical trials [12]. Kawanami et al. suggested that SGLT-2 inhibitors are effective in the management of diabetic nephropathy because of the reduction of glomerular hyperfiltration, oxidative stress, and inflammation [13].

Conclusion

A significant reduction in the urine ACR was seen in the group that was administered vildagliptin and Remogliflozin. On the other hand, the reduction in urine ACR in the group administered glimepiride and metformin was not significant. Hence, the combination of SGLT-2 inhibitors and DPP-4 inhibitors can help delay the renal complications of diabetes mellitus and improve the eGFR of such patients.

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