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Effect of SGLT2 and DPP4 Inhibitors on Urinary Albumin Excretion in Type 2 Diabetes Mellitus with Diabetic Kidney Disease Stage (1-4)

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ABSTRACT
Diabetic nephropathy, characterized by the presence of albuminuria, is one of the common complications of long-standing uncontrolled diabetes mellitus. Both Sodium-Glucose Co-Transporter 2 inhibitors and Dipeptidyl Peptidase 4 inhibitors are known to minimize the progression of albuminuria. We compared the efficacy of SGLT2 and DPP4 inhibitors on urinary albumin excretion along with blood glucose level. In this study, 30 subjects were randomly divided into two groups and prescribed SGLT2 inhibitors and DPP4 inhibitors, respectively, for 12 weeks. Urinary albumin-creatinine ratio was used as a biomarker and measured for every patient before and after the treatment. At the end of the study, SGLT2 inhibitors showed a better impact on urinary albumin excretion compared to DPP4 inhibitors with a p-value <0.01, and both oral hypoglycaemic agents have a similar impact on HbA1C.

Keywords: Diabetic Kidney Disease, Urinary albumin excretion, Albuminuria, SGLT2 inhibitors, DPP4 inhibitors.

I. INTRODUCTION

Diabetes mellitus is one of the largest global public health concerns.According to International Diabetes Federation(IDF),there were 537 million adults are living with diabetes in 2021, and expected that the number can escalate to 643 million by 2030.(1)Long lasting Uncontrolled diabetes mellitus can manifest microvascular and macrovascular complications. Diabetic Kidney Disease (DKD) isthe serious microvascular complication, the common cause of mortality among diabetes patients.(2)Albuminuria (UACR: >30 mg/g) is the hallmark of DKD and its progression can end up having End-Stage Renal Disease (ESRD) and fatal cardiovascular events.(3)Reduction of albuminuriais an appropriate therapeutic goal for reducing the progression of diabetic nephropathy.(3)

Sodium glucose co transporter 2 inhibitors (SGLT2 i) are oral hypoglycaemic agents with cardiovascular and renal benefits.(4)Dipeptidyl peptidase 4 inhibitors(DPP4 i) are another class of oral hypoglycaemic agents, works through incretin hormones responsible for haemostasis after food intake. (7) Some studies like **DAPA- CKD study by Niels Jongs et.al**,(5)**a study on Dapagliflozin by Sergei I Petrykiv et.al**,(6)a**study on DPP4 inhibitors by Young-gun Kim et. al**(8)and a **meta-analysis study on DPP4 inhibitors by Jae Hyun Bae et. al**,(9) has showed that both SGLT2 inhibitors and DPP4 inhibitors, significantly reduced urinary albumin excretion in albuminuria patients with or without diabetes mellitus.

There are no more studies which compares the difference between SGLT2 inhibitors and DPP4 inhibitors effect over albuminuria in DKD, the current study aimed to compare the difference betweenthe Reno protective effect of SGLT2 inhibitors and DPP4 inhibitors by using urinary albumin excretion as an indicator.

II. MATERIAL & METHODS

2.1: Study Design and Subjects: A prospective interventional comparativestudy was conducted inCARE Hospitals, Banjara Hills, Hyderabad, a tertiary care hospital in India.The study was approved bythe Institutional Ethics committee of Care Hospitals.

The Inclusion criteria of the study are as follows: (1) Type 2 DM patients who have UACR> 30mg/g with diabetic kidney disease – stage 1-4. (2)Patients with HbA1C ranging between 6.5% - 9%

Exclusion criteria of the study are as follows: (1) age less than18 years and who are not ambulatory. (2) Albuminuria by non-renal disease.(3) Type 1 Diabetes Mellitus (4) End-Stage Renal Disease. (5) who were previously on both SGLT 2 inhibitors and DPP 4 inhibitors.

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This study was a single site, double arm study aimed to compare the effect of SGLT 2 inhibitors and DPP 4 inhibitors on urinary albumin excretion in T2 Diabetes Mellitus with Diabetic Kidney Disease (1-4).A total of 30 patients were included in our study based on the inclusion and exclusion criteriaand with their consent. Study subjects were divided randomly and based on background therapy into two groups, one group of patients were prescribed SGLT2 inhibitors (Dapagliflozin 10 mg/day or Empagliflozin 25mg/day through oral route) and another group with DPP4 inhibitors(Teneligliptin 20mg/day or Vildagliptin 100mg/day through oral route)respectively. All subjects were counselled, not to change their lifestyle, diet plan and not to withdraw any ofthe prescribed drugs. After 12 weeks of therapy SPOT-UACR results were collected from all the subjects and compared with baseline SPOT-UACR values to observe the difference. Written informed consent was collected from all the patients before initiation.

2.2. Endpoint:

The primaryendpoint was the change in the mean of SPOT-UACR from baseline to week 12 in both groups. The secondaryendpoint includes changes in HbA1c from baseline to week 12.

2.3. Data extraction:

The date when the drug was initiated is termed as the initiation date and the date after 12 weeks of therapywas termed as the end date. SPOT-UACR sample at the beginning of study defined as baseline sample and at the end defined as a sample after therapy. All the demographic details of the subject were collected along with baseline laboratory testsincluding FBS, PPBS, HbA1c, Sr. creatinine, blood pressure, and history along with the duration of DM. The main parameter of the study SPOT-UACR was collected before initiation and after 12 weeks of therapy.

2.4. Statistical analysis:

Continuous variables are represented as mean and standard deviation wheredata follows a normal distribution. Categorical variables are represented asfrequencies and percentages. The statistical significance between the groups was accessed byt-test. Data were analysed using R studio.

III. RESULTS:

A total of 30 subjects, 19 male(63%) and 11 female (37%) withmean age of patients was 60.36 +_ 12.15 years were divided into two groups. one group subjects prescribed with Dapagliflozin 10 mg/day or Empagliflozin 25mg/day, another group subjects prescribed with teneligliptin 20mg/day or vildagliptin 100 mg/day for 12 weeks. Mean UACR of all subjects at baseline in both the groups were 456.4 mg/g and 420.7 mg/g respectively whereas mean HbA1c in two groups found to be 7.8% and 7.4% respectively.

Primary End Point:

One group of patients had a geometric mean UACR of 456.4 mg/g at baseline and 299.5 mg/g after 12 weeks of therapy with SGLT2 inhibitors. The geometric mean UACR significantly reduced by 156.9 mg/g (p = 0.0014).

Another group patients had mean UACR of 420.7 mg/g at baseline and 401.8 mg/g after 12 weeks therapy with DPP4 inhibitors. The mean UACR was reduced by 18.9 mg/g (p = 0.2343) which is not significant.

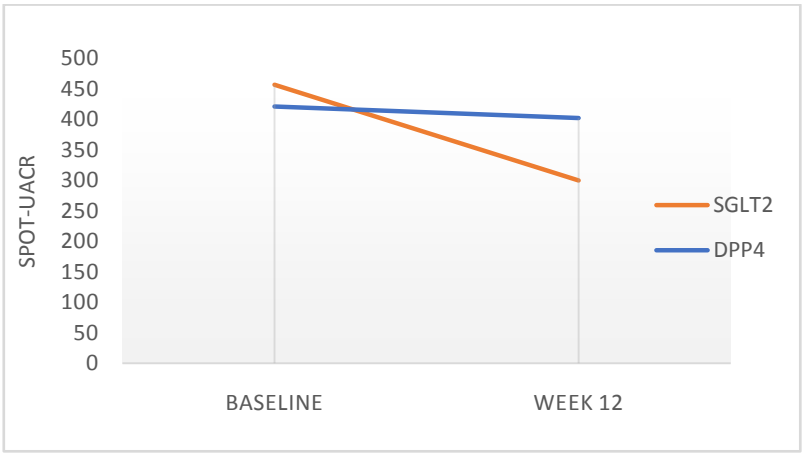

Fig 1: Changes in SPOT- UACR from baseline to week 12 in both groups. Statistical comparison for changes in mean from baseline to week 12 was conducted using t-test.

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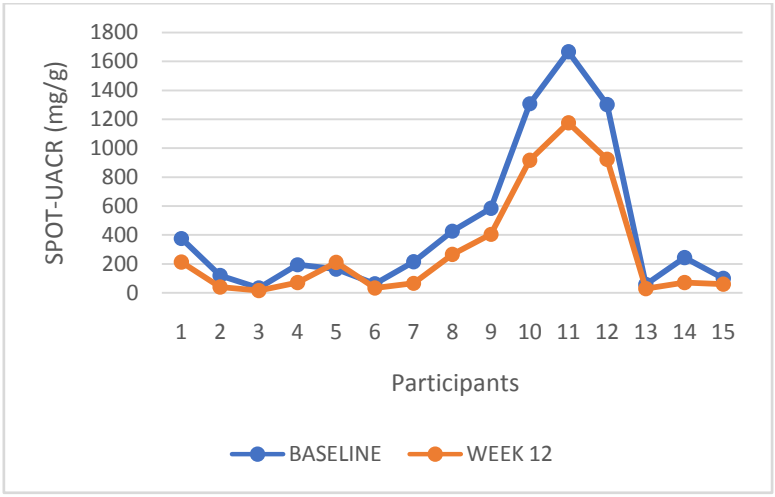

Fig 2: Changes in SPOT-UACR from baseline to week 12 after therapy with SGLT2 inhibitors. Data were expressed as individual measurements.

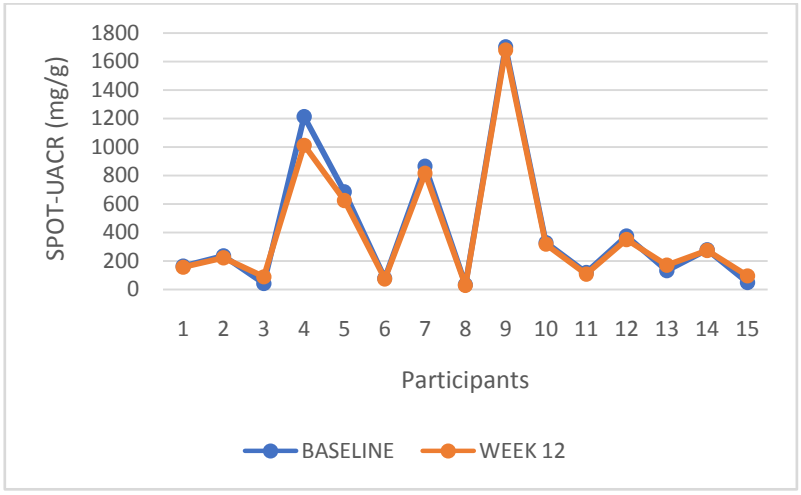

Fig 3: Changes in SPOT-UACR from baseline to week 12 after therapy with DPP4 inhibitors. Data were expressed as individual measurements.

HbA1c:

Patients treated with SGLT2 inhibitors had a mean HbA1c of 7.8% at baseline and 7.1% after 12 weeks therapy. After 12 weeks of therapy, SGLT2 inhibitors significantly reduced mean HbA1c by 0.7%.

Patients treated with DPP4 inhibitors had mean HbA1c of 7.4% at baseline and 6.9% after 12 weeks. DPP4 inhibitors has reduced mean HbA1c by 0.5% after 12 weeks.

Table 1: Changes in SPOT-UACR and HbA1c from baseline to week 12 after therapy with SGLT2 inhibitors. Data are expressed as geometric mean using t-test.

Variable	Baseline	Week 12	Difference	p-value
SPOT-UACR	456.4 mg/g	299.5 mg/g	-156.9 mg/g	0.0014
HbA1C	7.85 %	7.12 %	-0.73 %	

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Table 2: Changes in SPOT-UACR and HbA1c from baseline to week 12 after therapy with DPP4 inhibitors. Data are expressed as geometric mean using t-test.

Variable	Baseline	Week 12	Difference	p-value
SPOT-UACR	420.7 mg/g	401.8 mg/g	-18.9 mg/g	0.2343
HbA1C	7.4 %	6.9 %	-0.5 %	

Safety:

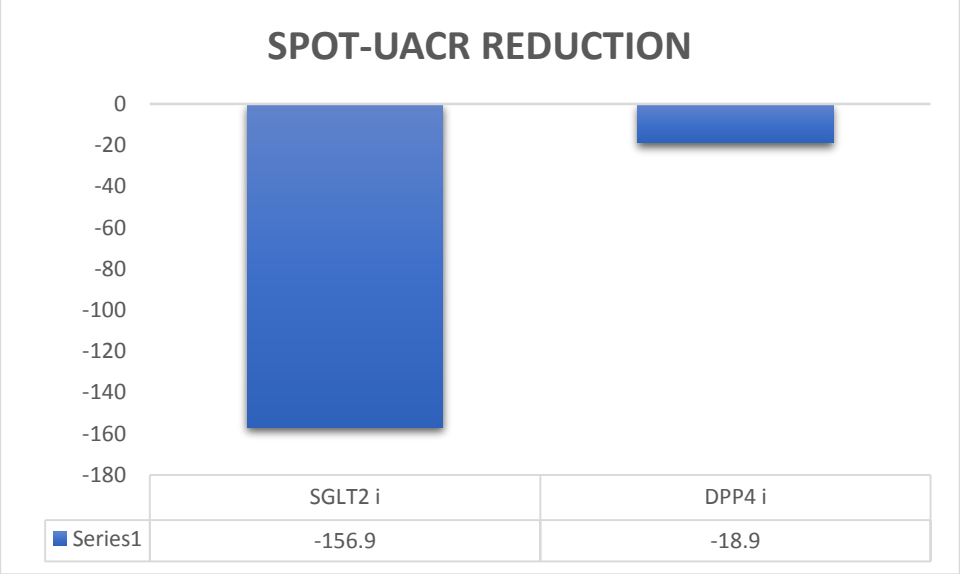
One patient treated with SGLT2 inhibitors reported with urinary tract infection. There were no reports of serious adverse effects found. In addition, there were no notable changes in laboratory test values associated with the safety of subjects.

IV. DISCUSSION:

Diabetic Nephropathy is one of the common complications of long-standing Uncontrolled Diabetes Mellitus. Albuminuriais the key marker of Diabetic Nephropathy and its progression can lead to End Stage Renal Disease

Analysis of global clinical trials suggests that inhibition of SGLT2 and DPP4 reduces UACR in both micro and macro albuminuria along with hyperglycaemic improvement. SGLT2 inhibition can reduce glomerular hyperfiltration through afferent vasoconstriction by exposing Sodium to maculadensa and controls the progression of Diabetic Nephropathy. In addition, DPP4 inhibition also plays role in nephroprotection by reducing oxidative stress, inflammation and improvement of endothelial dysfunction.

Present study was aimed to compare the effectiveness of SGLT2 inhibitors and DPP4 inhibitors in controlling Urinary Albumin Excretion and it was conducted prospectively where patients were prescribed with SGLT2 and DPP4 inhibitors for Diabetic kidney disease. A total of 30 Subjects were divided into two groups(15 each), one group prescribed with SGLT2 inhibitors and another group with DPP4 inhibitors for 12 weeks.After 12 weeks of therapy SPOT-UACR of all subjects was evaluated and compared with initial values.Data were statistically analysed using SPSS.Mean UACR values of patients treated with SGLT2 inhibitors before and after therapy were 456.4 mg/g and 299.5 mg/g respectively (-156.9 mg/g). Whereas patients treated with DPP4 inhibitors have reported mean UACR 420.7 mg/g before therapy and 401.8 mg/g after therapy (-18.9 mg/g). Patients treated with SGLT2 inhibitors have shown statistically significant improvement with **p value 0.0014.** Both SGLT2i and DPP4i has shown similar impact on HbA1C after 12 weeks of therapy.



V. LIMITATIONS:

1. The study did not take into consideration, patients with HbA1c >9%
2. Patients with prescribed anti-hypertensiveagents like ACE inhibitors and ARBs were excluded from the study.
3. The study did not take into consideration, patients with any kind of Urinary Tract infections.
4. The study did not take into consideration, subjects like pregnant women, End Stage Renal Disease patients, age <18 years.

VI. CONCLUSION:

In conclusion from the above study, after 12 weeks of therapy SGLT2 inhibitors reduced urinary albumin excretion bystatistically significant amount. Hence SGLT2 inhibitors found to be inferior to DPP4 inhibitors in terms of albuminuria reduction in Diabetic Nephropathy and both oral hypoglycaemic agents have shown similar impact on HbA1C.

CONTRIBUTION STATEMENT

All authors contributed equally in this study. S H and AVN S P worked on designing the study method, ethical committee approval, conducting the study, interpretation of data, and final paper writing. K V and A A were involved in enrolling patients for the study with consent, ethical approval, and data collection. P K NS dedicated his time and experience to this study by guiding the whole team throughout the study, being involved in designing the study methodology, and interpreting the data. L T was involved in protocol preparation and ethical committee approval.

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