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ASSOCIATION OF RENAL SAFETY PROFILE AND IMPACT OF ALBUMIN-TO-CREATININE RATIO OF DPP4 INHIBITORS COMPARED TO SULFONYLUREA IN DIABETIC KIDNEY DISEASE

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ABSTRACT

BACKGROUND: To analyze the potential impact of sulfonylurea (SU) and dipeptidyl peptidase-4 inhibitor (DPP4i) on the risk of significant renal events and the albumin to creatinine ratio in diabetic kidney disease. Here, were view the renal effects of DPP-4 inhibitors with special focus on its influence on the onset and progression of microalbuminuria by assessing albumin to creatinine ratio. We will discuss potential mechanism of these effects, the differences of action between sulfonylurea alone and addition of DPP-4 inhibitors to the treatment regimen, and future perspectives of its use in patients with diabetic kidney disease.

The aim of this study was to determine the Reno protective effects of DPP-4i, using albumin to creatinine ratio and glomerular filtration rate (GFR) as indicators, in diabetic kidney disease.

METHODS: In a single centre, an observational study was carried out and data from 120 patients were evaluated. The main factors that were evaluated utilizing case report form were the ADA diagnostic criteria, ACR (albumin to creatinine ratio), HbA1c value, and GFR (glomerular filtration rate). The investigation was conducted at the NG Hospital and Research Centre, Coimbatore. The study was carried out in the general medicine department and intensive care unit of the hospital over a period of 6 months from March 2023 to September 2023.

CONCLUSION: DPP-4 inhibitors have a favorable effect profile, with minimal treatment-limiting adverse effects. These inhibitors are also known for their cardiovascular and renal safety, making them a preferred choice, particularly in patients with diabetes chronic kidney disease.Our study demonstrated that patients using DPP-4 inhibitors showed better outcomes compared to those using sulfonylurea alone for managing DKD.

INTRODUCTION

Diabetic kidney disease (DKD) represents one of the most frequent microvascular complications of diabetes, with an overall prevalence of approximately 40% in the type 2 diabetes population. [1] DKD is defined by the presence of albuminuria and decreased glomerular filtration rate (GFR) into 5 chronic kidney disease (CKD) stages. Normal GFR and urine results (mostly albuminuria) or kidney structural abnormalities are indicative of stage 1 CKD. GFR values are used to determine stages 2-4. In comparison to individuals without diabetic kidney disease (DKD), patients with DKD, especially at stage 1, have a much higher risk of cardiovascular problems and hypoglycemia. Several studies have demonstrated a strong correlation between poor glucose management in both type 1 and type 2 diabetes and the risk of diabetic kidney damage. [2] [3]. The increasing prevalence of diabetes worldwide, leading to a steep rise in patients with chronic complications, represents one of the major health problems of the current medicine. One of the interesting possibilities that have emerged from experimental studies is the renoprotective effect of DPP-4 inhibitors on diabetic kidney disease. [4]. Metformin-sulfonylurea (Met-SU) is a common pharmacological treatment for the management of diabetes. [5]

For type 2 diabetes, metformin is the first-line medication that lowers blood sugar (T2D). Metformin has shown in a number of experimental investigations to reduce renal inflammation, oxidative stress, and fibrosis in diabetic kidney disease (DKD). Clinical research has demonstrated that the use of metformin in T2D patients with chronic kidney disease (CKD) is linked to lower risks of death, cardiovascular disease, and the development of end-stage renal disease (ESRD). However, because metformin may raise the risk of lactic acidosis, it should be used cautiously in individuals with CKD. [6]

A family of antidiabetic drugs known as dipeptidyl peptidase-4 (DPP-4) inhibitors increases the activity of incretin by slowing

down the breakdown of glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1.Although they have been used safely in individuals with chronic kidney disease, DPP-4 inhibitors have an unknown impact on renal outcomes. Dipeptidyl peptidase-4 (DPP-4) inhibitors used to treat type 2 diabetes may have nephroprotective benefits in addition to the lower kidney risk that comes with glycemic management, according to emerging data. [7] Preclinical research revealed that DPP-4 inhibition has pleiotropic effects that may be advantageous to the kidneys. [8] [9] [10] In the current investigation, we used an observational research design to examine the impact of DPP-4 inhibitors on the renal outcomes of individual patients with type 2 diabetes and DKD in comparison to metformin or other sulfonylureas. The aim of our study is to determine and compare the efficacy and safety of DPP4 inhibitors over sulfonylurea in type II diabetes mellitus and assessing their additional effects in improving GFR and ACR in CKD patients.

i. Compare clinical efficacy using ADA diagnostic criteria, ACR, and GFR in patients -PRIMARY OUTCOME
ii. Compare safety profile of sulfonylurea and DPP4 inhibitors -SECONDARY OUTCOME.

MATERIALS AND METHODS:

The investigation was conducted at the NG Hospital and Research Centre, Coimbatore. The study was carried out in the general medicine department and intensive care unit of the hospital over a period of 6 months from March 2023 to September 2023. A detailed proposal of this study was submitted to the institutional ethical committee and approval was obtained. A total of 153 cases were included in this study out of which 120 patient came for both the reviews.

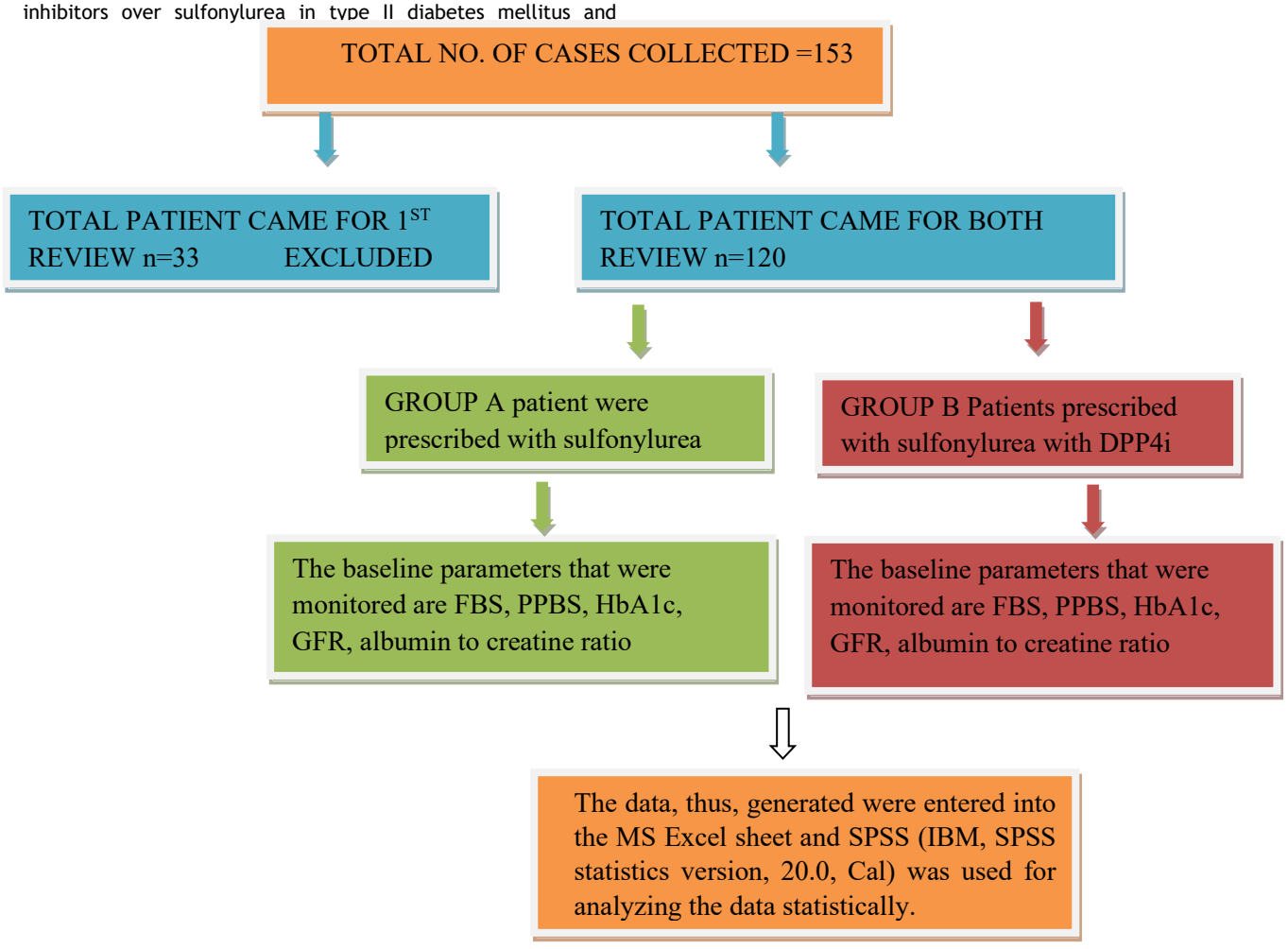

Figure 1: Illustration Of The Floor Diagram On Research Methodology

SELECTION CRITERIA:

INCLUSION

- Both male and female patients
- Patient diagnosed as CKD based on radiological and biochemical parameters
- Patients with age between 18 to 80 with newly diagnosed as well as K/C/O type II DM
- All inpatients have been included with higher diagnostic parameters of DM and CKD
- All patients with HbA1c more than 6.5%

EXCLUSION

- Patients with type I DM impaired glucose tolerance, metabolic syndrome and Gestational diabetes have been excluded
- Patients with any co morbidities as listed are excluded from study like cancer, newly onset diabetes after organ transplant or recent cardiovascular event
- Patients who are having H/O adverse events like pancreatitis or hypoglycemia.

RESULTS

In this observational study the majority of patients were male 87 i.e 72.5% and female 33 (27.5%) were found to be less effected

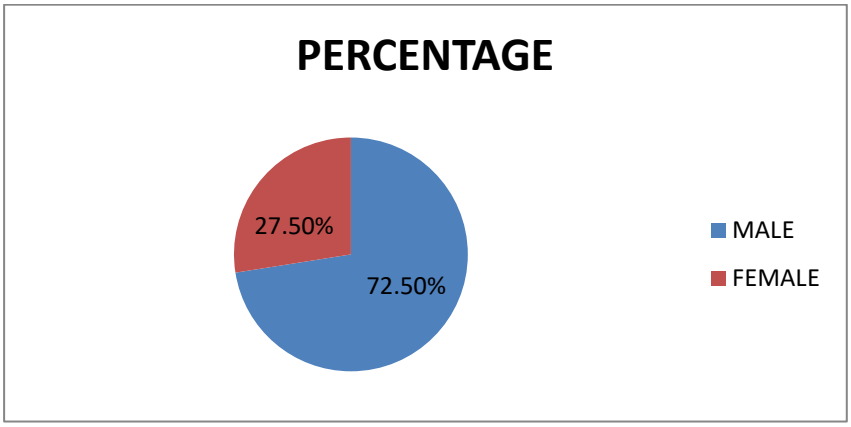

Figure 2-Distribution based on gender demographics among the study population (*n*=120)

In this observational study the majority of patients belongs to age group of 51-60 i.e 66 (55%) . other age groups were found to be less effected as compared.

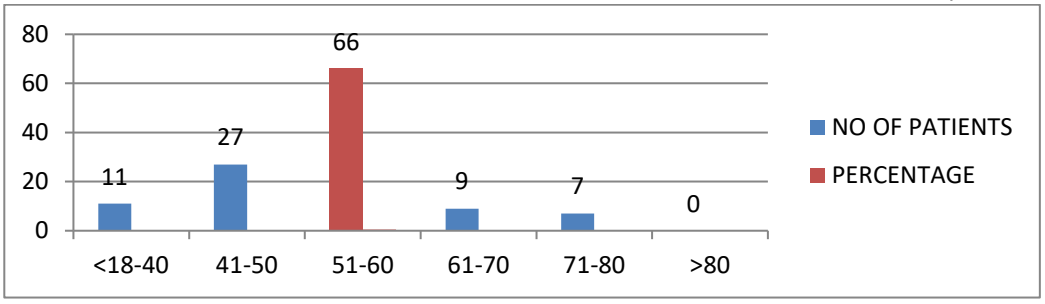

Figure -3 Age wise distribution of study population (*n*=120)

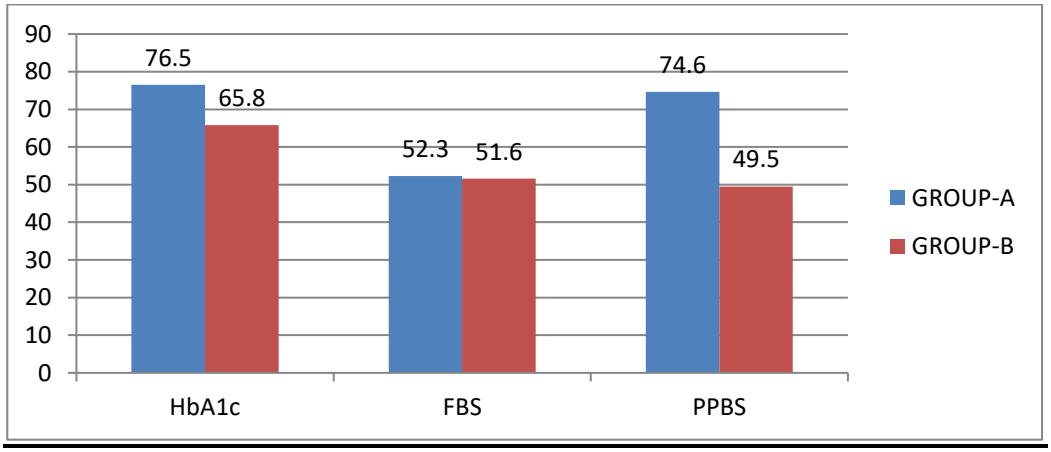

Figure-4 Mean HbA1c, FBS, PPBS of GROUP A and GROUP B among the study population n=120

MEAN	GROUP A	GROUP B
ACR	22.43	16.84
GFR	57.4%	69.6%

Table -1 Mean ACR ratio in GROUP A and GROUP B among study population (n=120)

By this mean value analysis we found that there was an improvement in GFR value in group A and group B ie 57.4% to 69.6% which is almost an improvement of 12 % when DPP4i was added .Simultaneously, there was also and improvement in albumin to creatinine ratio when group A and group B was compared. There was a decline in albuminuria risk when DPP4i was used .

STATISTICAL ANALYSIS

In our study, out of 120 patients, paired t test one tailed and two tailed was performed assuming that our data follows normal distribution curve.

Table -2 p Value of Each Parameter

SL.NO	PARAMETER	P VALUE
1	HbA1c	0
2	FBS	0.07*(not significant)
3	PPBS	0
4	GFR	0.000044
5	ACR	0.019

From the above statistical analysis we found that HbA1c, PPBS,GFR, and ACR p vaule was statistically significant and FBS p value was not statistically significant

DISCUSSION

The findings revealed that the participant in this study (*n*=120) were male 87 (72.5%) and female 33(27.5%) hence, males are under high risk of diabetes induced CKD as compared to female patients. This finding is similar to previous study by Oskar Swartling et al 2021found that men had a higher risk of progression, a steeper eGFR decline, and a higher risk of death, especially cardiovascular mortality, prior to that of women. [6]

In this study the majority of participant comes under the age group 51-60 years 66 (55%). This result is consistent with a 2014 research by Valma Harjutsalo et al. that indicated that kidney function decreases after age 50 by around 1 mL/minute year.[7]

While assessing HbA1c mean value of GROUP A (76.5%). Metformin can lower hemoglobin A1c (HbA1c) levels by 1–2% when used as a monotherapy or in combination with other anti-diabetic drugs. In one study, metformin monotherapy decreased mean HbA1c by 1.3% after 29 weeks, compared to a 0.4% increase in the placebo group. The American Diabetes Association (ADA) recommends metformin to treat type 2 diabetes and maintaining HbA1c levels below or around 7%. Metformin is considered a "foundation therapy" for T2D patients who don't achieve their glycemic targets through diet and other lifestyle changes.was found to be higher than GROUP B (65.8%). This finding is similar to previous study by Awadhesh K singh et al 2020 conducted, which summarizes the HbA1c lowering effect from different meta analysis in comparison of sulfonylurea plus metformin with DPP-4i [8]

While assessing we found that PPBS mean percentage of GROUP A patients (74.68%) were significantly higher, but there was a visible decline in PPBS mean value of GROUP B patient(49.55%) after introduction of DPP-4 inhibitors. This result is consistent with Biswanath Sharma's earlier research. In a 2019 research by Sarkar et al., there was a substantial ($p<0.001$) drop in mean FBS, PPBS levels, and HbA1c% from the baseline in both groups.[9]

While assessing we found that ACR mean value of GROUP A patients(22.43). After initiation we found that there was significant reduction in ACR mean value of GROUP B patients (16.84) after initiation of DPP-4 in the regimen. This finding is similar to previous study by Young Gun Kim et al 2016 conducted a retrospective cohort study. He observed that the mean ACR in all patients increased approximately 39 mg/g from 1 year before DPP-4i treatment to the point of DPP-4i treatment initiation, while it was decreased approximately 45 mg/g 1 year after initiation of DPP-4i treatment. [10]

While assessing we found that there was significant decline in GFR mean value in GROUP B(96.6%) as compared to GROUP A(57.4%). This finding is similar to previous study by Wan Chia Hsu et al 2022 Young Gun Kim et al 2016 in which a total of 2202 patients were enrolled. The incidence of eGFR decline ≥30% from the baseline was 10.08% in the DPP-4 inhibitor group and 16.17% in the non-DPP-4 inhibitor group.[10][11]

LIMITATIONS OF THE STUDY

A total of 153 patients were enrolled in this study out of which only 120 patient's data were precise which other 28 patients were not available for GROUP B review. Missing patient's data had lead to a gap in the study findings potentially acquiring the accuracy and the reliability of results.

There was variability in dosage and adherence among the drugs which contributed to add variability and complicating the analysis of safety and effectiveness.

FUTURE RECOMMENDATIONS

Metformin can be used when the eGFR is ≥45 mL/min/1.73 m^2. (2) If the eGFR is 30–44 mL/min/1.73 m^2, do not start metformin treatment. If metformin is already in use, administer a daily dose of ≤1,000 mg. (3) Metformin is contraindicated when the eGFR is <30 mL/min/1.73 m^2.A study found that long-term treatment with metformin can cause a slow but progressive increase in albumin-to-creatinine ratio (ACR). ACR is a clinical outcome predictor that reflects urinary albumin excretion. In the study, metformin use resulted in a 20.9% increase in ACR compared to other comparators. The study also found that among patients entering with ACR less than 30 mg/g, the 4-year cumulative incidence of albuminuria was highest with metformin (22.5%) compared to rosiglitazone (18.2%). Albuminuria is the earliest clinically detectable stage of diabetic nephropathy. It can signal renal microvascular disease and increase the risk of cardiovascular disease morbidity and mortality. The higher the level of albuminuria, the greater the risk

CONCLUSION

DPP-4 inhibitors have a favorable effect profile, with minimal treatment-limiting adverse effects. These inhibitors are also known for their cardiovascular and renal safety, making them a preferred choice, particularly in patients with diabetes chronic kidney disease.Our study demonstrated that patients using DPP-4 inhibitors showed better outcomes compared to those using sulfonylurea alone for managing DKD.

CONFLICT OF INTEREST AND FINANCIAL SUPPORT

As much as it looks promising in theory, the lack of resources is a significant challenge to overcome. Since sufficient finance cannot be established, integral goals cannot be met and jeopardize the long-term sustainability of the project and there was no significant conflict of interest.

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