

Evaluation of Efficacy of SGLT-2 Inhibitors in Diabetic Nephropathy

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ABSTRACT:

Diabetes is a global epidemic causing severe problems around the world. It is one of the leading causes to Diabetic nephropathy which is also known as Diabetic kidney disease. It is caused due to increased levels of blood glucose due to improper insulin secretion in beta cells. Here, SGLT-2 is the new class of drugs and advanced treatment for diabetic nephropathy. They have fewer side effects and are effective in treating diabetic nephropathy. Our study aims to determine the efficacy of SGLT-2 inhibitors in treating patients with diabetic nephropathy when compared with other anti-diabetic treatment. A prospective interventional study with a sample size of 450 patients in a period of 4 months was conducted in which about 214 members were filtered as per inclusion criteria and exclusion criteria. Clinical data of patients (>30 years) of tertiary care hospital, who had received anti-diabetic treatment for DM and other co morbidities was collected. According to our study results were found to be statically significant with SGLT2 Inhibitors having more cure rate (44.60%) when compared with other anti-diabetic drugs having cure rate (25.66%). There is no significant difference across males and females and empagliflozin have more increase in eGFR. Our study shows that, Patients treated with SGLT-2 Inhibitors have more increase in eGFR value than with other anti- diabetic drugs and treatment with SGLT2 Inhibitors is more beneficial with less side effects when compared to other anti- diabetic treatment.

KEY WORDS: eGFR, SGLT-2 inhibitors, CKD, DKD, ESRD, hyperglycemia.

I. INTRODUCTION:

Diabetes mellitus (DM), a group of metabolic diseases caused due to increase levels of

blood sugar ^[1]. A chronic, multi-system, non-communicable disease creating epidemic havoc ^[2]. DM stands at 9th position in Global Burden of Disease in 1999, ranking 4th in 2017^[3]. Impaired insulin secretions and resistance to tissue or both together contribute to pathophysiology. This in-turn lead to low secretion of pancreatic beta cells causing many complications of diabetes ^[4]. The long-term effects of hypoglycemia is associated with failure of different organs like eyes (retinopathy), kidneys (nephropathy), nerves (neuropathy) and cardiovascular system ^[5]. Of these, Diabetic nephropathy, a micro-vascular complication causing mortality and morbidity is a kidney disease occurs due to long standing diabetes, results from specific pathological, structural and functional changes in diabetic patient resulting in clinical data represented by changes in proteinuria, hypertension and decreased function of kidneys. It mainly affects tiny blood vessels in glomerulus, composed of capillary blood vessels, that becomes difficulty in filtration of blood ^[6], main feature of DN is increase in urinary albumin excretion (UAE) ^[7], measuring albumin urea ^[8], urinary albumin/creatinine ratio ^[9], estimated glomerular filtration rate (eGFR)^[10,11], cystatin-C ^[12] are commonly used parameters in diagnosing the renal failure. The most frequent cause of End-Stage Renal Disease (ESRD) in many countries has resulted from diabetes ^[13]. Glomerular filtration, the first step in urine filtration, is the passive process of ultra-filtration of plasma from blood into bowman's space as it transverse the Glomerular capillaries. GFR varies by body size, so it is indexed relative to an average body surface are (BSA) of 1.73m²/ml/min. The mean value is approximately 120-130ml/min/1.73m² for adults younger than 40 years of age and decline with age ^[14]. GFR cannot be measured directly, it can be assessed from clearance measurements or estimated

from serum levels of endogenous filtration markers such as creatinine or cystatin-C [15, 16]. Creatinine is a breakdown product of creatinine phosphate produced by muscles in a fair rate depending on body muscle mass [17]. eGFR is calculated from serum creatinine, which monitors the progression of renal disease. If the serum creatinine is greater than the normal level, it is diagnosed as renal failure [18]. To measure eGFR, MDRD formula is used and it requires serum creatinine, age ethnicity and albumin levels.

MDRD formula for creatinine:

$eGFR = 186 \times [sr.cr (mg/dl)]^{-1.154} \times age (years)^{-0.203} \times (0.742 \text{ if females})$. The units for eGFR are ml/min/1.73m². Increased serum creatinine levels and decreased creatinine clearance are the parameters in the patient which shows the abnormal function of kidneys.

The main goal of treatment is to prevent the progression of declined renal function from macro-micro-albuminuria and occurrence of CV events. In general, to delay DN progression, adequate metabolic control and hemodynamic abnormalities means lowering blood glucose levels and blood pressure stops the progressive of Diabetic Kidney Disease (DKD)/DN [19]. Till now the oral anti diabetic drugs like biguanides, gliptins

etc are used for the control of this disease, whereas recently FDA approved class SGLT-2 inhibitors are used to control the nephropathy. Sodium glucose co-transport type-2 inhibitors are the new class of antidiabetic agents reducing plasma glucose by inhibition of glucose uptake in renal proximal tubules [20-23]. These are the novel drugs for the diabetic patients as they not only target major pathophysiological defects in T2DM such as resistance to insulin and insulin secretion, they also plays a key role in reabsorption of glucose in the kidneys, representing a potentially promising option for diabetes treatment [24]. In DN, protection of kidneys is major and very important since DM induced kidney disease is the major precipitating cause for renal replacement therapy. SGLT-2 inhibitors possess more reno-protection properties by 8 molecular mechanisms and protects against renal failure [25]. They work completely independent of insulin hormone and functions according to prevailing serum glucose levels, therefore carries a negligible risk of hypoglycemia [26]. Apart from potent hypoglycemic effects they also exert other effects like weight loss [27], decreased blood pressure [28], reduced uric acid levels [29], attenuation of oxidative stress [30], anti-inflammatory action and improve fibrosis [31].

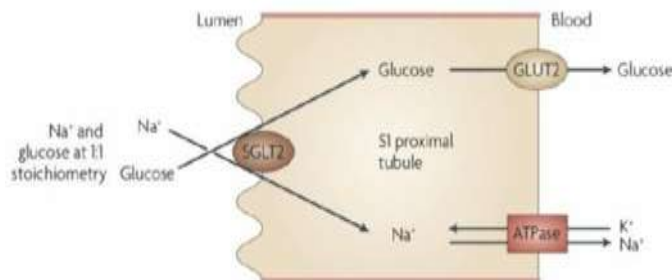


Figure: SGLT-2 mediates glucose reabsorption in kidneys [32].

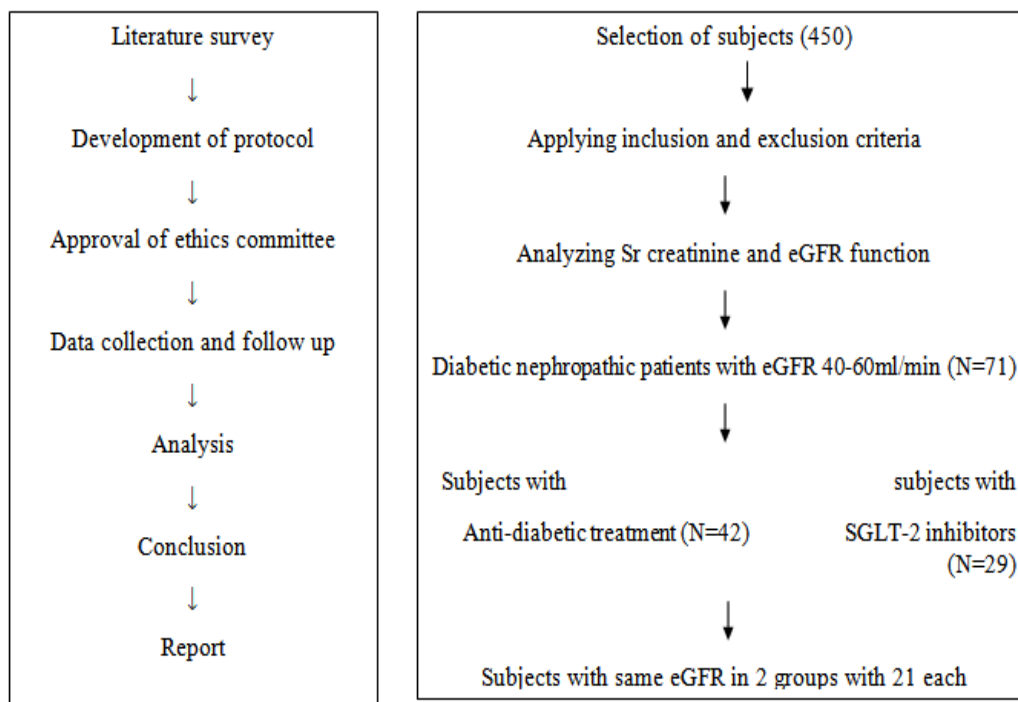
II. MATERIALS AND METHODS:

Through a prospective medical record review, a total of 450 patients with type 2 diabetes diagnosed with diabetic nephropathy and other comorbidities, aged between 30-40 years old with an eGFR range of 40-60ml/min/1.73m². The subjects were recruited from September 2019 to February 2019 and scheduled for follow-up from November for every two months. The subjects were explained regarding the study before considering them into the study and their consent were taken with their signature. This study was conducted at Tertiary care hospital, Hyderabad. The ethical committee approval was taken from the hospital. The patients that are excluded from the

study includes the following- age below 30 years and above 80 years, De-novo DM, pregnancy and lactating women, gestational diabetes and patients with other malignancies. The data we collected includes patients demographic details like- name, age, gender, admission number, laboratory details like- FBS, PPBS, HbA1C, serum creatinine value, GRBS etc, treatment chart. Diabetic nephropathy was assessed by eGFR value using serum creatinine value with the help of MDRD equation.

The main objective of this study is to determine the efficacy of SGLT-2 inhibitors in diabetic nephropathy patients when compared to the other anti-diabetic drugs, use of eGFR in

diagnosing the diabetic nephropathy and to improve the quality of life of patient.



Ethics committee approval: yes, KIMS/EC/2019/44-07

III. RESULTS AND DISCUSSION:

In our study we have collected 450 cases of DM with Diabetic nephropathy. As per inclusion and exclusion criteria, from these 450 patients we got 71 patients with eGFR range between 40-60ml/min. Treatment was given randomly with SGLT2 Inhibitors and other anti-diabetic drugs for 71 patients. Among 71 patients, 29 patients were treated with SGLT2 Inhibitors and 42 patients were treated with other anti-diabetic drugs. Based on eGFR range we have considered equal eGFR from

both groups, and then we got 21 patients from SGLT2 Inhibitors and 21 patients from other anti-diabetic drugs. We have followed up these cases for every one month continued for 4 months. We have evaluated the collected data into various factors based on age, gender, comorbidities, therapy, and serum creatinine and eGFR values. We have analyzed the data of patients who were treated SGLT2 Inhibitors and other anti-diabetic drugs, Illustration based on No. of patients and eGFR values.

Demographics and comorbidities of patients are summarized in table 1.

CHARACTERISTIC		71 SAMPLES N (%)	42 SAMPLES N (%)
GENDER	Male	41 (57.7%)	22 (52.3%)
	Female	30 (42.2%)	20 (47.6%)
AGE GROUP	31- 40	1 (1.40%)	00 (0%)
	41- 50	1 (1.40%)	01 (2.3%)
	51-60	11 (15.49%)	07 (16.6%)
	61-70	46 (64.78%)	28 (66.6%)
	71-80	12 (16.90%)	06 (14.2%)
COMORBIDITIES	DM	23 (32.39%)	15 (35.7%)
	DM + HTN	13 (18.30%)	09 (21.4%)
	DM + Hypothyroidism	04 (5.63%)	02 (4.76%)
	DM+ CAD	04 (5.63%)	03 (7.14%)

DM+ HTN+ CKD	04 (5.63%)	02 (4.76%)
DM+ CKD	08 (11.26%)	03 (7.14%)
DM+ CKD+ CAD	04 (5.63%)	02 (4.76%)
DM+ CKD+ CVA	01 (1.40%)	00
DM+ AKI	01 (1.40%)	00
DM+ HTN+ CKD+ COPD	01 (1.40%)	00
DM+ HTN+ Hypothyroidism	04 (5.63%)	03 (7.14%)
DM+ CKD+ HTN+ CVA	01 (1.40%)	01 (2.38%)
DM+ HTN+ CKD+ CAD	01 (1.40%)	00
DM+ HTN+ CAD	01 (1.40%)	01 (2.38%)
DM+ CVA	01 (1.40%)	01 (2.38%)

According to gender, out of 71 cases, females were found to be 30 (42.2%) in which 12 (40%) are prescribed with Sgl2 Inhibitors and 18 (60%) are prescribed with other anti-diabetic treatment in the case of males 41 (57.7%), 17 (41.4%) are prescribed with SGLT2 Inhibitors and 24 (58.5%) are treated with anti-diabetic treatment.

Depending upon the age a greater number of patients were found between the age group of 61-70.

Patients with Diabetes (23), diabetes in combination with other diseases like HTN (13), are higher.

LABORATORY PARAMETER		71 SAMPLES			42 SAMPLES		
		Before	After 1 st Review	After 2 nd Review	Before	After 1 st review	After 2 nd review
Serum Creatinine (mg/dl)	<0.80	00	01	07	00	00	04
	0.80- 0.89	00	05	10	00	04	07
	0.90- 0.99	00	12	11	00	09	06
	1.0- 1.09	07	04	10	04	02	08
	1.10- 1.19	08	14	07	08	07	04
	1.20- 1.29	09	10	06	05	06	04
	1.30- 1.39	16	04	07	09	02	03
	1.40- 1.49	08	09	05	05	04	02
	1.50- 1.59	08	03	02	02	02	02
	1.60- 1.69	05	02	00	02	02	00
	1.70- 1.79	08	01	00	06	00	00
	1.80- 1.89	02	01	01	01	01	01
	>1.90	00	05	03	00	03	01

There is a decrease in serum creatinine level for every review. There is an Improvement in patients' condition with therapy. Before treatment 16 patient's serum creatinine values are between

(1.30-1.39), at the time of 1st review 14 patient's serum creatinine level has decreased to (1.10-1.19), 11 patients were having serum creatinine level between (0.90-0.99) at the time of 2nd review.

eGFR value(ml/min)		Before treatment		After 1 st review		After 2 nd review	
		N= 71	N= 42	N= 71	N= 42	N= 71	N= 42
Standard	<40	00	00	05	03	03	01
	40- 45	18	08	04	02	02	02
	45.1- 50	10	03	05	02	01	01
	50.1- 55	06	05	12	04	05	00

	55.1- 60	08	05	03	02	09	05
	>60	00	00	13	08	22	12
SGLT2	<40	00	00	00	00	00	00
	40- 45	08	08	02	01	00	00
	45.1- 50	04	03	05	05	03	03
	50.1- 55	10	05	03	03	04	03
	55.1- 60	07	05	05	03	01	01
	>60	00	00	14	09	21	14

When it comes to Egfr levels before treatment 18 members of antidiabetic treatment are under 40-45ml/min and 10 patients of sgl2 are under (50.1-55), at the time of 1st review 13 patients of antidiabetic treatment and 14 sgl2 patients egfr levels have increased above 60 ml/min and at the time of 2nd review 22 patients of antidiabetic treatment and 21 sgl2 patients egfr levels have increased above 60 ml/min.

✓ **Above 71 cases are filtered into 42 cases and these cases are divided into 2 groups each group contains 21 subjects with equal eGFR values before initiation of therapy (N=42)**

Depending on gender wise distribution of patients, out of 42 cases males were found to be more i.e. 22 (52.3%) cases compared to females 20 cases (47.6%).

Based on age, a greater number of patients are under age group of 61-70 (28).

Diabetes and diabetes with HTN are leading comorbidities with 15 (35.7%) and 09 (21.4%) number of patients respectively.

For the sample size of 49 patients, before treatment, Serum creatinine values of 9 patients are between 1.3-1.39, at the time of first review, 9 patients were having serum creatinine values

between 0.90- 0.99, and 8 patients were having serum creatinine values between 1.0- 1.09 at the time of 2nd review. Overall there is a decrease in serum creatinine levels for every review.

For the sample size of 49 patients, 8 patients with both SGLT2 Inhibitors and standard therapy are within the eGFR range of 40-45 ml/min before treatment, at the time of 1st review 9 patients of SGLT2 Inhibitors and 8 patients of Standard therapy are lying between eGFR above 60 ml/min. 14 SGLT2 Inhibitors and 12 Standard therapy patients are having eGFR above 60 ml/min at 2nd review.

STATISTICAL ANALYSIS:

All data are expressed as mean ± standard deviation with 95% confidence interval. The categorical variables were tested using independent student's t- test and one-way ANOVA by using SPSS Software.

Statistical analysis of serum creatinine values, eGFR levels and efficacy among SGLT2 Inhibitors is done by independent student's t- test and the statistical analysis of demographics of patients with treatment is done by using one-way ANOVA.

Sr Creatinine value (mg/dl)	Treatment	N	Mean ± SD
Before treatment	Total	71	1.37±0.22
	SGLT2 Inhibitors	29	1.34±0.22
	Others	42	1.40± 0.21
After 1 st review	Total	71	1.26± 0.35
	SGLT2 Inhibitors	29	1.14± 0.25
	Others	42	1.34±0.39
After 2 nd review	Total	71	1.10±.30
	SGLT2 Inhibitors	29	0.99±0.24
	Others	42	1.18± 0.32
Before treatment	Total	42	1.34±0.22
	SGLT2 Inhibitors	21	1.34±0.22

After 1 st review	Others	21	1.34± 0.24
	Total	42	1.24± 0.37
	SGLT2 Inhibitors	21	1.15± 0.24
After 2 nd review	Others	21	1.34±0.45
	Total	42	1.08±0.29
	SGLT2 Inhibitors	29	1.00±0.24
	Others	42	1.15± 0.33

eGFR values	Treatment	N	Mean ± SD	P value
Before treatment	Total	71	49.36± 6.2	0.068
	SGLT2 Inhibitors	29	51.00±6.31	
	Others	42	48.22 ± 6.10	
After 1 st review	Total	71	57.82 ± 16.7	0.067
	SGLT2 Inhibitors	29	62.20 ±14.01	
	Others	42	54.80±18.00	
After 2 nd review	Total	71	66.58 ±17.59	0.008
	SGLT2 inhibitors	29	73.17±18.31	
	Others	42	62.04± 15.73	
Before treatment	Total	42	49.52±6.63	1.000
	SGLT2 Inhibitors	21	49.52±6.72	
	Others	21	49.52±6.72	
After 1 st review	Total	42	57.38±15.06	0.137
	SGLT2 Inhibitors	21	60.85±14.03	
	Others	21	53.90±15.57	
After 2 nd review	Total	42	66.92±17.65	0.05
	SGLT2 Inhibitors	21	71.61±18.87	
	Others	21	62.23±15.37	

SL.NO	DRUG	MEAN ±SD (BEFORE)	MEAN±SD (AFTER)	PERCENTAGE INCREASE	P VALUE
1	Empagliflozin(n=19)	52.00± 5.42	75.26±18.65	44.7	0.0001
2	Dapagliflozin(n=08)	48.00± 7.76	68.00±19.00	41.66	0.0231
3	Remogliflozin(n=02)	53.50±7.77	75.00±12.72	40.18	0.0902

SOURCE	SUM SQUARES	OF	Df (Degrees of freedom)	MEAN SQUARES	OF	P VALUE
GENDER	264.372		1	264.372		0.415
AGE	6017.221		26	231.432		0.875

Treatment* GENDER	379.105	1	379.105	0.332
Treatment* AGE	706.347	10	70.635	0.995
GENDER* AGE	1797.307	11	163.392	0.921
Treatment* GENDER* AGE	0.158	1	0.158	0.984

As the patient was receiving the treatment, serum creatinine values were decreasing. P values of 71 samples before treatment was 0.137, P value at the time of 1st Review 0.019, P value at the time of 2nd Review 0.007.

The eGFR values of the patients have increased as treatment commences. P values of 71 samples before treatment is 0.068 and no patient was having eGFR above 60ml/min, P value at the time of 1st Review is 0.067 here few patient 's eGFR levels was above 60ml/min i.e. 14 SGLT2 Inhibitors and 13 Anti diabetic patients were observed. P value at the time of 2nd review is 0.008. For the sample of 42 patients P value before treatment is 0.098, p value at the time of 1st Review is 0.0104, and P value at the time of 2nd Review is 0.0103. P value before treatment is 1.000, P value at the time of 1st Review is 0.137, and P value at the time of 2nd Review is 0.05.

IV. CONCLUSION:

In conclusion, the SGLT-2 inhibitors when given to patients, there is a better increase in eGFR of patients when compared to patients in a group who are treated with other anti-diabetic drugs. There were significant difference in eGFR values of patients who are taking SGLT-2 inhibitors compared to the other anti-diabetic drugs. Thus SGLT-2 inhibitors may be preferred as a choice of treatment for patients diagnosing with nephropathy to enhance public health and high quality of life of affected people. Further studies with larger samples has to be executed to verify similar results and more outcomes and to decide the need of SGLT-2 inhibitors in diabetes and diabetic nephropathy.

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