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An Update on Current Usage of SGLT2-Inhibitors in Diabetic Kidney Disease: Special Focus on Dapagliflozin

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Diabetic Kidney Disease (DKD) is one of the most serious long-term outcomes in patients with T2DM. Prevalence of DKD is predicted to increase as the prevalence of diabetes is growing rapidly thereby leading to substantial morbidity and mortality. Established therapies still focus on effective glycemic control and blood pressure control, to arrest disease progression and regression of albuminuria. SGLT2 Inhibitors are a novel class of oral hypoglycaemic agents that increase urinary glucose excretion by suppressing glucose reabsorption at the renal proximal tubule. SGLT2 inhibitors lower HbA1c and improve various metabolic parameters including BP, lipid profile, albuminuria and uric acid. Clinical trials have shown that SGLT2 inhibitors improve cardiovascular

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and renal outcomes and mortality in patients with T2DM, thereby garnered considerable attention in the recent past and are considered potential first-line candidates for the management of T2DM and has emerged as a cardio-renal game-changer.

Keywords: Diabetic kidney disease; sodium glucose co-transporters 2 inhibitors; dapagliflozin.

ABBREVIATIONS

International Diabetes Federation, IDF; Sodium Glucose Transporter Inhibitor, SGLTi; Chronic Kidney Disease, CKD; Diabetic Kidney Disease, DKD; Heart Failure, HF; Glomerular Filtration Rate, GFR; hospitalization for Heart Failure, hHF; Type 2 Diabetes Mellitus, T2DM; Angiotensin Converting Enzyme, ACE; Angiotensin Receptor Blockers, ARB; Mineralocorticoid Receptor Antagonists, MRA; Renin Angiotensin Aldosterone System, RAAS; End Stage Renal Disease, ESRD; New York Heart Association, NYHA; Glycosylated Haemoglobin, HbA1C; Urinary Albumin Creatinine Ratio, UACR; American Diabetes Association, ADA; Kidney Disease: Improving Global Outcomes, KDIGO; End Stage Renal Disease, ESRD.

1. INTRODUCTION

"In the arena of chronic non-communicable disease, diabetes is one of the fore-runners in global health related emergencies of the current century which has reached to worrying levels. Diabetes is a major health issue and as far as the latest IDF 2021 data is concerned, around half a billion people in the world are living with diabetes" [1].

"Over the last few decades, the load of diabetes patients has steadily increased in India and across the world, with India contributing a major part of the burden. In India, the National Health Policy in 2017 aims to increase screening and treatment of 80% of people with diabetes and reduce premature deaths from diabetes by 25% by the year 2025" [2].

"One of the most common and severe complications of Diabetes is Diabetic Kidney Disease (DKD) and it is associated with increased morbidity and mortality in those patients. The prevalence of DKD is also predicted to increase as the prevalence of diabetes is growing rapidly in developing countries. If there is no immediate improvement in the clinical strategy for prevention of DKD, the mortality too is expected to rise. Diabetes additionally increases the cardiovascular mortality risk in patients with kidney disease" [3,4].

"The reported prevalence of Chronic Kidney Disease (CKD) in different regions in India ranges from < 1% to 13%. The recent data from the International Society of Nephrology's Kidney Disease Data Center Study reported a prevalence of 17%. Etiology of CKD varies considerably throughout India" [5].

1.1 Aim

Several recent articles have thrown light on the benefits of SGLT2i and their role in the changing paradigm of Diabetic Kidney Disease management. This review article is an attempt to conglomerate briefly the current therapies in DKD management with special focus on Dapagliflozin and related clinical guidelines.

2. METHODOLOGY

This being a narrative review, we did not conduct a systematic literature search. A search of the PubMed database was conducted in November 2022, with no date limits, using the search terms "Diabetic Kidney Disease", "Sodium Glucose Transporters 2 Inhibitors", "Dapagliflozin" and "Treatment" and the results were screened for relevance to the review the topic. Articles were also added based on the authors' knowledge of the area.

2.1 Pathophysiology and Classification of Diabetic Kidney Disease

Diabetic Kidney Disease is a complex entity and still clinical research are still going on to know the exact process and pathogenesis behind it. Multiple theories are proposed histopathologically. The clinical outcomes are poor because of limited information. The most conventional therapy aims at good glycemic control and blood pressure control. These have been unable to stop DKD progression to ESRD and kidney related mortality. The need to improve the understanding and searching the exact pathogenic mechanisms of DKD is

important in developing newer strategies for treating those affected. The newer theories have mentioned about different pathways and mediators involved in the development and progression of DKD. The natural history of DKD [6] is described as Fig. 1.

As far as the classification of CKD is concerned, according to 2022 ADA/KDIGO Guidelines [7], 3 important criteria are taken into consideration viz., e-GFR, Albuminuria and Cause. Based on the degree of e-GFR and albuminuria, staging of CKD is as Fig. 2.

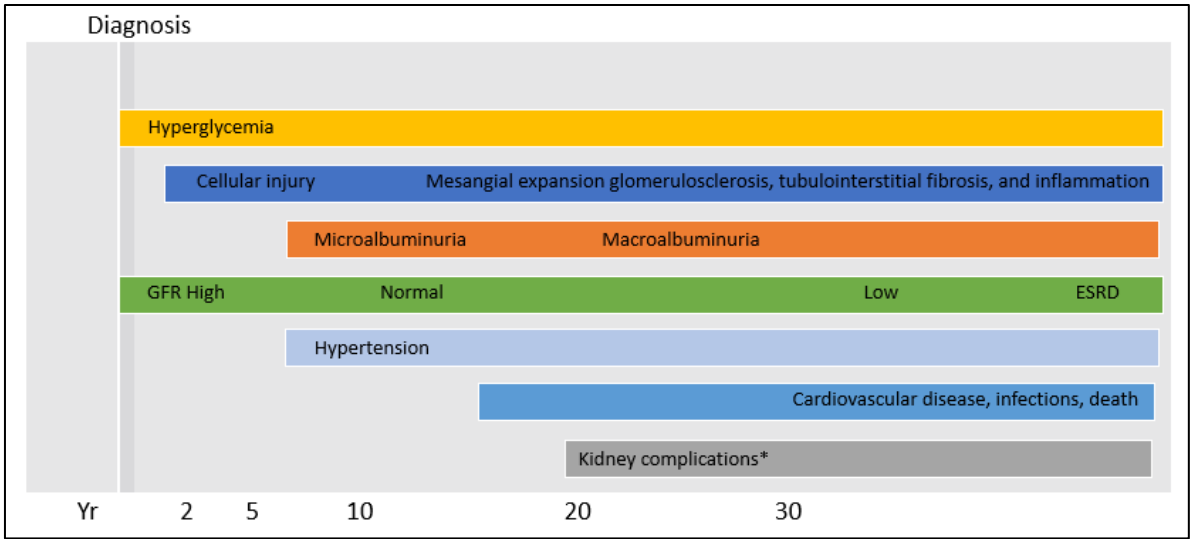

Fig. 1. Conceptual model of the natural history of diabetic kidney disease
(Adapted from Alicic. Clin J Am Soc Nephrol. 2017 Dec 7;12(12):2032-2045)

Prognosis of CKD by GFR and Albuminuria Categories

GFR categories (ml/min/1.73 m²) Description and range				Albuminuria categories Description and range		
				A1	**A2**	**A3**
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-299 mg/g 3-29 mg/mmol	≥300 mg/g ≥30 mg/mmol
	G1	Normal or high	≥90			
	G2	Mildly decreased	60-90			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk.
KDIGO 2012

Fig. 2. Stages of CKD based on e-GFR and albuminuria
Green reflects no evidence of CKD by eGFR or albuminuria, with screening indicated once per year. For monitoring of prevalent CKD, suggested monitoring varies from once per year (yellow) to 4 times or more per year (i.e., every 1–3 months, [deep red]) according to risks of CKD progression and CKD complications

2.2 Screening of Diabetic Kidney Disease

In patients suffering from Diabetic Kidney Disease, clinically the first feature to be detected is albuminuria. Albuminuria is followed by decreased kidney function in the form of decreasing e-GFR and increase in serum creatinine. Hence, albuminuria and e-GFR assessment remains the gold standard in screening and diagnosing patients with DKD.

"The ADA 2022 Standards of Medical Care Practice Guidelines recommends screening Annually starting from diagnosis for everyone with type 2 DM by measuring renal function and albuminuria; whereas in type 1 DM, it starts after 5 years of diagnosis. Patients with albuminuria should undergo an evaluation regarding the presence of comorbid associations, especially retinopathy and macrovascular disease" [8].

"The ADA/KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease recommends for patients with type 2 DM and CKD using HbA1c to monitor glycemic control in patients with diabetes and CKD at least twice per year" [7].

2.3 Conventional Management of Diabetic Kidney Disease

The conventional therapy still focuses on good glycemic control and blood pressure control, to target DKD progression and regression of albuminuria. Multiple studies have shown that albuminuria regression in diabetic individual can result in better renal and cardiovascular outcomes. The best management of CKD in diabetes needs a multidisciplinary and cross-functional team effort. Involvement of multiple stakeholders like the diabetologist, nephrologist and cardiologist is important to ensure a holistic approach to manage these cases. A comprehensive strategy in CKD should be applied to reduce the risk of kidney disease progression and cardiovascular disease simultaneously. Following are the management options in DKD (Table 1) [7].

2.4 Blood Pressure Management and the Role of RAAS Inhibitors in Diabetic Kidney Disease

"The beneficial effects of RAAS blockade were shown to extend to patients with severely increased albuminuria. Two landmark trials, the Irbesartan Diabetic Kidney Disease (IDNT) [9] and the Reduction of Endpoints in NIDDM (non-insulin-dependent diabetes mellitus) with the Angiotensin II Antagonist Losartan (RENAAL) [10] studies, were conducted in patients with T2D and CKD, having albuminuria greater than 1 g/d. In the IDNT trial, treatment with irbesartan compared with placebo resulted in a 33% decrease in the risk of doubling of serum creatinine concentration and was independent of blood pressure. In the RENAAL trial, losartan significantly reduced the incidence of doubling of serum creatinine, ESKD, and death, each by 16% compared with placebo. Amongst hypertensive patients with T2DM and persistent albuminuria, treatment with an ARB significantly reduces the rate of progression to clinical albuminuria".

"An ACEi or ARB, should be initiated in patients with concomitant diabetes, hypertension, and albuminuria, with titration to the highest tolerated approved dose. The KDIGO 2021 expert consensus suggest that adults with high BP and CKD be treated with a target systolic blood pressure (SBP) of <120 mm Hg, using standardized office BP measurement. The recommendations came with an objective that in most patients with CKD, a cardiovascular event is a more likely outcome than End Stage Kidney Disease. The RAAS inhibitors (ACEi or ARB) should be used in patients with CKD and albuminuria irrespective of their diabetes status and evidence for their use in moderate to severe proteinuria is particularly strong" [11]. This recommendation places a high value on the potential benefits of RAAS blockade with ACEi or ARBs for slowing the progression of CKD in patients with diabetes.

2.5 Glycemic Control and the Role of SGLT2 Inhibitors in Diabetic Kidney Disease

One of the primary targets for controlling the progression of worsening renal functioning in individuals with Diabetes and CKD is Glycemic Management. The management of hyperglycaemia in CKD, especially those accompanied by slowing of e-GFR decline is a challenge. The management requires a more specific understanding, especially in relation to the choice of drug that is to be used. The approach is individualised according to the stage of the disease and associated co-morbidities. SGLT2 Inhibitors are a novel class of oral hypoglycaemic agents that increase urinary glucose excretion by suppressing glucose

reabsorption at the renal proximal tubule along with natriuresis which leads to Tubuloglomerular feedback and hence leads to a maladaptive glomerular afferent arterial vasodilatation and increased intraglomerular pressure. That leads to renal protection by increasing the renal blood flow. The ADA/KDIGO 2022 Clinical Practice Guidelines recommends an individualized HbA1c target ranging from <6.5% to <8.0% in these patients [7].

2.6 SGLT2 Inhibitors: A Standard of Care in the Management of Diabetic Kidney Disease

"SGLT2 inhibitors lower HbA1c without increasing the risk of hypoglycemia, induce weight loss and improve various metabolic parameters including BP, lipid profile, albuminuria and uric acid. Several clinical trials have shown that SGLT2 is (empagliflozin, dapagliflozin and canagliflozin) improve cardiovascular and renal outcomes and mortality in patients with type 2 diabetes. Effects of SGLT2i on the kidney can be explained by multiple pathways. It is believed that SGLT2is may improve renal oxygenation and decrease intra-renal inflammation which thereby slows the progression of kidney function decline. SGLT2 inhibitors have garnered considerable attention in the recent past and are considered potential first-line candidates for the management of T2DM. The recently published data has highlighted benefits of SGLT2 inhibitor like Dapagliflozin and Empagliflozin in heart failure and chronic kidney disease, irrespective of diabetes status – and has emerged as a cardio-renal game-changer" [12].

Table 1. Management of DKD

Life style Modifications	Pharmacotherapy			
Healthy Diet Physical Activity, Smoking Cessation, Weight Management	**Glycemic Control** Metformin, SGLT2 Inhibitors, GLP1 Receptor Agonists	**Blood Pressure Management** Renin-Angiotensin-Aldosterone System (RAAS) Inhibitors	**Lipid Management** Statins Therapy	**Others** Mineralocorticoid Receptor Antagonists, Endothelial Receptor Antagonist

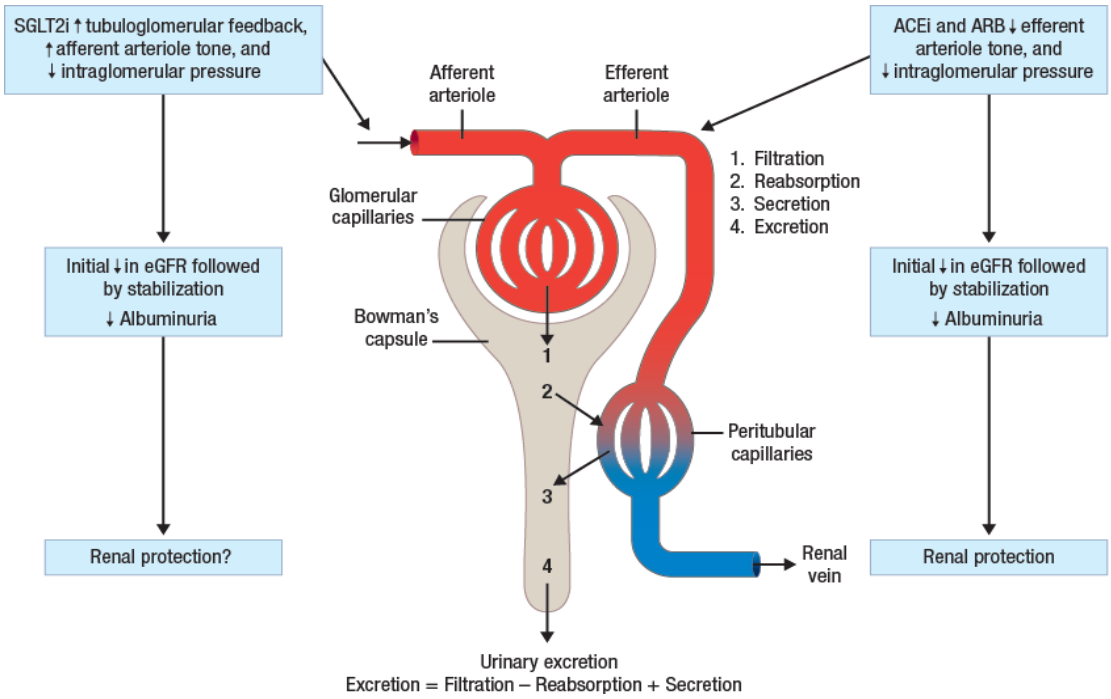

Fig. 3. Mechanism of Action of SGLT2 Inhibitors and RAAS Blockers (Adapted from Perkovic, et al., CMRO. 2015;31:2219-2231)

ACEi; Angiotensin Converting Enzyme inhibitor; ARB, Angiotensin Receptor Blocker; eGFR, estimated Glomerular Filtration Rate; SGLT2i, Sodium Glucose Co-Transporter 2 Inhibitor

The first CV outcome trials involving SGLT2 inhibitors enrolled patients with T2DM who had atherosclerotic cardiovascular disease (ASCVD) or were at very high risk for ASCVD but generally did not have CKD, although there was some overlap. Subsequent trials have shown that in addition to reducing CV risk in patients with T2D and CKD, SGLT2 inhibitors significantly reduce the risk of progressive kidney disease. In trials examining kidney benefits, patients were on clinically appropriate doses of RAAS inhibition, in the form of ACEI or ARB, prior to being started on SGLT2 inhibitors.

"In the CANVAS trial, patients were randomised to canagliflozin or placebo groups; the primary outcomes were nonfatal myocardial infarction (MI), non-fatal stroke and death from CV causes. 17.2% patients had a history of DKD, and in the final analysis there was 40% reduction in the kidney composite outcome (reduction in eGFR, kidney replacement therapy, or kidney death). There was also a 27% reduction of progression of albuminuria was also statistically significant" [13].

"The Dapagliflozin Effect on Cardiovascular Events trial (DECLARE-TIMI 58 trial) evaluated the CV outcomes with Dapagliflozin. The kidney outcomes were also evaluated to further investigate the effects on kidney related parameters. This trial randomized the patients to receive either dapagliflozin or placebo. The kidney outcome composite was defined as a >40% decrease in eGFR to <60 mL/min/1.73 m2, ESKD or death from kidney or cardiovascular cause. A reduction of 34% in the renal composite along with a 47% reduction of the individual components were seen" [14].

"In the EMPA-REG OUTCOME trial, patients with type 2 DM and a high CV risk patient were evaluated on Empagliflozin and placebo. The primary composite outcome of death from CV causes, nonfatal MI or nonfatal stroke were evaluated from this trial also. The kidney related outcomes were evaluated in a separate report. The outcomes of rate of doubling of serum creatinine level accompanied by an eGFR ≤45 mL/min/1.73 m2 initiation of kidney replacement therapy, or death from renal cause, was found to be 46% lower with empagliflozin as compared to placebo" [15].

The quest for better clinical outcomes and trial endpoints had led to the Dedicated Renal Outcome trials such as DAPA-CKD [16], CREDENCE [17] and the EMPA-KIDNEY [18]. These trials have enrolled various patient populations irrespective of Baseline characteristics like Diabetic status, Worsening renal function or underlying pathophysiology of kidney disease. The results were impressive from both the trials thereby extending the benefits of SGLT2i therapy to different patient profiles.

"As far as the Anti-diabetic therapy is concerned, the ADA 2022 guidelines recommends to consider the use of SGLT2 inhibitors in T2D patients with CKD" [4]. "The ADA/KDIGO 2022 guidelines recommends SGLT2 inhibitors (SGLT2i) for T2D and CKD, when eGFR is ≥ 20 ml/min per 1.73 m2 and with Metformin when eGFR ≥ 30 ml/min per 1.73 m2 an initial approach for management" [7].

"Renal function should be assessed prior to initiation of Dapagliflozin therapy and then as clinically indicated. A higher dose of the drug, Dapagliflozin 10 mg is indicated for prevention of renal outcomes and can be used in eGFR <25 ml/min to reduce the risk of eGFR decline and ESRD, while Empagliflozin can be used till eGFR less than 30 mL/min. In patients with volume depletion, correction of this condition prior to initiation of Dapagliflozin is advised" [19]. While using SGLT2 inhibitors in patients with T2DM, some important sick day rules are to be adhered to such as stopping the medications when the patient is having diarrhoea, vomiting or fever (unless only minor) until the patient is well and eating normally again. SGLT2 inhibitors causes increased risk of genital mycotic infections or UTI. Patients should be monitored and treat if indicated.

2.7 Clinical Evidence with Dapagliflozin in Diabetic Kidney Disease

"It all started with DECLARE-TIMI 58 [14] trial whereby the effects of Dapagliflozin was noticed in prevention and reducing the progression of kidney disease compared with placebo in this large and diverse population of patients with T2D with and without established atherosclerotic cardiovascular disease, most of whom had preserved renal function thereby benefitting the cardio-renal endpoints".

In DECLARE-TIMI 58, dapagliflozin also had demonstrated a favourable effect on UACR and renal-specific outcome across baseline UACR categories, including patients with normal albumin excretion. The results suggest a role for SGLT2i also in the primary prevention of diabetic kidney disease.

Table 2. Salient features of imp clinical trials with SGLT2 inhibitors

	DAPA-CKD [16]	CREDENCE [17]	EMPA-KIDNEY [18]
Molecule studied	Dapagliflozin 10 mg	Canagliflozin 100 mg	Empagliflozin 10 mg
Sample Size	4304	4401	6609
Asian patients (%/n)	(34.08%/1467 pts)	(19.9%/877 pts)	(34%/2244 pts)
Non-DM population (%/n)	(32.48 %/1398 pts)	None	(54%/3570 pts)
Lower limit of eGFR (mL/min/1.73 m^2)	25	30	20
Primary Endpoints	39% ↓	30% ↓	28% ↓
Secondary Endpoints	44% ↓	34% ↓	14% ↓
CV death or hHF	29% ↓	31% ↓	16% ↓ (NS)
All-cause mortality	31% ↓	17% ↓ (NS)	13% ↓ (NS)

GFR – Glomerular Filtration Rate; hHF: Hospitalization for heart failure; NS: Non-significant

Patients with CKD have an increased risk of heart failure during the course of disease. The DAPA-HF [20] trial which had heart failure outcomes as primary outcomes also evaluated the renal endpoints as additional secondary endpoints in the form of worsening renal function. The sub-group analysis of Dapagliflozin across different trials have also shown individualized end-points across certain set of patient population. The outcomes further delineate that the effect of Dapagliflozin is valid across overall patient population.

"In a prespecified analysis from the DAPA-CKD Trial, Jongs N et. al analysed that in patients with CKD with or without T2D, dapagliflozin significantly reduced albuminuria, with a larger relative reduction in patients with T2D. Though similar effects on clinical outcomes in patients with or without T2D is seen, but different effects on Urine Albumin-to-Creatinine Ratio (UACR) suggest that part of the protective effect in patients without diabetes is mediated through pathways that was unrelated to UACR reduction" [21]. "In another pre-specified analysis of DAPA-CKD Trial, Heerspink HJL et al. showed that dapagliflozin significantly slowed long-term eGFR decline in patients with CKD compared with placebo. The mean difference in eGFR slope between patients treated with dapagliflozin versus placebo was greater in patients with T2D, higher HbA1c, and higher UACR" [22].

As CKD progresses, the renal function tends to decline along the course of the disease, more so in high-risk patients. A timely intervention before reaching this stage can increase the overall survival of the CKD patients and has been shown by SGLT2 inhibitors [23].

To show whether Dapagliflozin has similar effect in reducing kidney and cardiovascular events independent of baseline glycemic status, Persson F et.al, has shown that participants irrespective of their glycemic status have similar outcomes [24]. As far as baseline diabetes medications are concerned, pre-specified analysis of DAPA CKD trial has shown that dapagliflozin has reduced kidney and CV events in T2DM with CKD independent of baseline diabetes drug class or number [25]. A prespecified analysis of Dapagliflozin in non-diabetic individuals (HbA1C<6.5%) from two trials viz. DAPA-CKD and DAPA-HF shows that there is reduced incidence of New-Onset Diabetes [26]. Thus, dapagliflozin has shown its beneficial effects across a diverse set of patient population independent of their glycemic status or baseline medications which they are on.

2.8 Guidelines Supporting the Usage of SGLT2 Inhibitors in Diabetic Kidney Disease

"The 2022 AACE Clinical Practice Guidelines recommended the use of a SGLT2i with proven benefit as foundational therapy for persons with T2D and CKD with eGFR ≥ 20 ml/min per 1.73 m2 to reduce progression of CKD and risk of CVD" [27]. "The guidelines also mentioned the use of Renin-angiotensin-aldosterone system blockade with an ARB or an ACE inhibitor for persons with albuminuria (T1D or T2D) to reduce risk of DKD or CKD in DM progression" [27].

The ADA 2022 Guidelines recommends the use of SGLT2 inhibitors additionally for cardiovascular risk reduction in T2DM patients and CKD when e-GFR and UACR values are ≥25 mL/min/1.73 m2 or ≥300 mg/ g, respectively [7]. The KDIGO 2022 Clinical Practice Guidelines recommend for patients with T2D and CKD with

an eGFR ≥ 20 ml/min per 1.73 m2 to be started with SGLT2i and eGFR ≥ 30 ml/min per 1.73 m2 to be started on Metformin after lifestyle therapy, as needed for glycemic control [8].

3. DISCUSSION

Diabetic Kidney Disease patients are typically older, with longer period of diabetes, and a lot of comorbidities. The prevalence of DKD in India is 34.4 % according to one study [28]. The therapeutic management of DKD is typically multi-factorial, which include tight glycemic management, blood pressure management, lipid-lowering agents, weight loss and smoking restriction. All patients with diabetes should be screened annually for decreased e-GFR and UACR to identify chronic kidney disease. To assess the success of treatment, the clinical markers in the progression of DKD must be known. Few patients may have Diabetic Kidney Disease with minimal proteinuria. Slowing the progression of DKD can be challenging even with the latest and best treatment options available. Majority of patients with diabetes and CKD have high residual risks of CKD progression and cardiovascular disease despite treatment. These patients are often at a high risk for kidney failure, atherosclerotic cardiovascular disease, heart failure, and premature mortality. Clinical trials have rendered support for new approaches to risk reduction. Drugs like SGLT2 inhibitors have significantly reduce the risk of progression of composite kidney outcomes, including worsening kidney function, end-stage kidney disease, and cardiovascular-related or kidney-related death seen in trials. The ADA recommends SGLT2 inhibitors in patients with established CKD to reduce their risk of progressive kidney dysfunction, in addition to background RAAS inhibitor therapy.

4. CONCLUSION

Managing patients with Diabetic Kidney Disease remains a clinical challenge and inspite of current therapies there exists substantial long-term morbidity and mortality. Chronic diseases like DKD and ESRD have an increased healthcare expenditure on family and society. There's an ever evolving need to improve the understanding of DKD to develop best and affordable management approaches to delay DKD in future. The use of therapies that prevent or reverse organ injury may represent a comprehensive strategy to reduce disease burden which will be more successful in combination with the traditional approaches. The robust data for SGLT2 inhibitors from clinical trials and real-world clinical practice has clearly established their role in the management of Diabetic Kidney Disease in the days to come.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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